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(21) International Application Number: PCT/KR95/00183 (22) International Filing Date: 29 December 1995 (29.12.95) (30) Priority Data: 1994/38787 29 December 1994 (29.12.94) KR (71) Applicant (for all designated States except US): SUNKYONG INDUSTRIES CO., LTD. [KR/KR]; 600, Jungja-1 dong, Jangan-ku, Suwon-si, Kyungki-do 440-301 (KR). (72) Inventors; and (75) Inventors/Applicants (for US only): PARK, Pyeong-Uk [KR/KR]; Hyundai Apartment 20-603, Apgujong-dong, Kangnam-ku, Seoul 135-110 (KR). PYO, Sungsoo [KR/KR]; Jugong Apartment 702-402, Byulyang-dong, Gwacheon-si, Kyungki-do 427-040 (KR). LEE, Ki-Seung [KR/KR]; Dongsin Apartment 206-409, Jungja-1 dong, Jangan-ku, Suwon-si, Kyungki-do 440-301 (KR). GAM, Jongsik [KR/KR]; Jugong Apartment 254-101, 4, Wonmoon-dong, Gwacheon-si, Kyungki-do 427-030 (KR). SUNG, Jin, Heung [KR/KR]; Dosigyebal Apartment 901-106, Gayang-dong, Kangseo-ku, Seoul 157-200 (KR). PARK, Jung, Soo [KR/KR]; 40-14, Jungja-2 dong, Jangan-ku, Suwon-si, Kyungki-do 440-302 (KR). PARK, Don, Soo [KR/KR]; Samsung Apartment 7-206, Gwonsun-dong,	Gwonsun-ku, Suwon-si, Kyungki-do 441-390 (KR). RYU, Keun, Ho [KR/KR]; Jugong 2 Area Apartment 118-402, Maetan-dong, Suwon-si, Kyungki-do 442-370 (KR). PARK, Jeong, Ho [KR/KR]; 568-15, Pajang-dong, Jangan-ku, Suwon-si, Kyungki-do 440-290 (KR). (74) Agent: HUH, Sang, Hoon; Namyong Building, 5th floor, 809-16, Yeoksam-dong, Kangnam-ku, Seoul 135-707 (KR). (81) Designated States: AU, BR, CA, CN, HU, JP, NO, PL, RU, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. With amended claims.	
(54) Title: NOVEL THIAZOLIDIN-4-ONE DERIVATIVES (57) Abstract <p>The present invention relates to novel thiazolidin-4-one derivatives having formula (I), which inhibit platelet-activating factor and/or 5-lipoxygenase for the prevention or treatment of inflammatory and allergic disorders mediated by platelet-activating factor and/or leukotrienes, and to pharmaceutical compositions containing these compounds, and to the use thereof to inhibit PAF and/or leukotriene. A process for preparing these compounds is also included in the present invention, wherein n, T, Q, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are respectively as defined in the description.</p> <div style="text-align: center;"> </div>		

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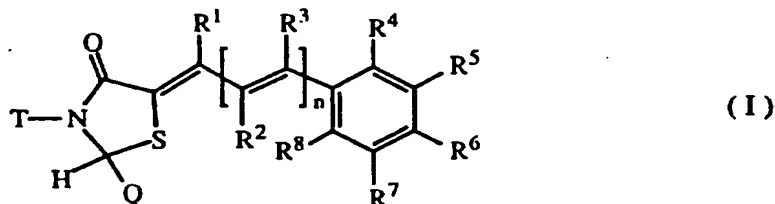
NOVEL THIAZOLIDIN-4-ONE DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

5 The present invention relates to novel thiazolidin-4-one derivatives having the following formula(I), which inhibit platelet-activating factor and/or 5-lipoxygenase for the prevention or treatment of inflammatory and allergic disorders mediated by platelet-activating factor and/or leukotrienes, and to pharmaceutical compositions containing these compounds, and to the use thereof to inhibit PAF and/or leukotriene.

10 A process for preparing these compounds is also included in the present invention.



wherein, n, T, Q, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are respectively defined as the below.

15

Description of the Related Art

Benveniste et al. found a factor in 1972 which strongly induces platelet aggregation from rabbit basophils. This factor was named platelet-activating factor (hereinafter referred to PAF). Hanahan et al. indentified the factor in 1980 as a
20 phosphoglyceride of the alkyl ether type having an acetyl group in the 2-position, i. e. 1-O-hexadecyl or octadecyl-2-acetyl-sn-glycerol-3-phosphocholine.

The physiological roles of PAF have been intensively investigated, and it is known that PAF is an important factor acting on platelet aggregation, reduction in blood pressure, immediate allergic reaction, contraction of smooth muscle,
25 inflammation, pain, edema, and alternation in the respiratory and circulatory systems. Therefore, PAF-antagonistic activity-possessing compounds are very useful for

treating various PAF-induced diseases, such as inflammatory diseases, allergic diseases, anaphylatic shocks, septic shocks, vascular diseases as DIC, myocardial diseases, asthma, pulmonary edema, and adult respiratory diseases.

Leukotrienes, like PAF, are potent lipid mediators of a variety of topical and systemic diseases and disorders. A 5-lipoxygenase in cytoplasm catalyzes the conversion of arachidonic acid to leukotriene A₄ which is the precursor of leukotriene B₄ and C₄. Leukotriene B₄ and C₄ are oxygenated metabolites that contribute to the pathogenesis of such inflammatory disorders as arthritis, asthma, psoriasis, and thrombotic disease. Leukotrienes are released concomitantly from leukocytes with PAF from a common phospholipid precursor upon cellular activation and act synergistically with PAF in many biological models.

It has been demonstrated by O'Donnell and Lewis et al. that a physical combination of a PAF antagonist and leukotriene inhibitor is significantly more effective than either agent alone in treating asthma in an animal model [Therapeutic Approaches to inflammatory Diseases, Lewis et al., Elsevier, New York, 1989, pp 169-193]. Shen et al. and Page et al. pointed out that single compounds which possess the dual inhibitory activity of PAF and leukotriene inhibition would have greater anti-inflammatory activities than a physical combination of a PAF and a leukotriene inhibitor. [PAF and Related Lipid Mediators, Plenum Pub., N.Y., 164 (1987) ; Trends in Pharmacol. Sci., 10(1989)].

Moreover, the chemical combination of PAF and 5-lipoxygenase inhibitory activities in one molecule has advantages over drug combinations in terms of optimal pharmacokinetics, clinical applications and developmental costs.

Under these circumstances, various thiazolidin-4-one derivatives have been synthesized. But thiazolidin-4-one compounds simultaneously possessing PAF-antagonistic activity and leukotriene inhibition activity have not been known at this time.

Reports related to thiazolidin-4-one derivatives are as followings: *N*-(phenyl,

pyridyl)-2-pyridyl-thiazolidin-4-one derivatives for agricultural chemicals [Japanese Patent Kokai No. 145679/79]; *N*-(phenyl, benzyl, cycloalkyl)-2-pyridyl-thiazolidin-4-one derivatives for agricultural chemicals [Japanese Patent Kokai No. 55184/80]; *N*-(carboxycyclohexylmethyl)-2-pyridyl-thiazolidin-4-one derivatives for
5 anticomplementary activity [Japanese Patent Application Kokai No. 85380/82]; *N*-(carboxymethylphenyl)-2-pyridyl-thiazolidin-4-one derivatives having anti-inflammatory and analgesic activity [Japanese Patent Kokai No. 88170/82]; *N*-(pyrazinyl)-2-pyridyl-thiazolidin-4-one derivatives for agricultural chemicals [Japanese Patent Kokai No. 183689/83]; *N*-(phenyl)-2-pyridyl-thiazolidin-4-one
10 derivatives for intermediates in synthesis [U.S. Patent No. 4,501,746]; *N*-(carbamoyloxy)-2-pyridyl-thiazolidin-4-one derivatives for cardiogenic [Japanese Patent Kokai No. 103883/86]; *N*-(alkyl, aminoalkyl)-2-pyridyl-thiazolidin-4-one derivatives for PAF-antagonist [Japanese Patent Kokai No. 126391/87, 139304/87, 160481/87, 12379/88 and European Patent Application No. 292305/88] etc..

15 Because of the large number of diseases and disorders which are mediated by PAF and leukotrienes, synthesis of new compounds which possess leukotriene or PAF inhibitory activity, and preferably compounds which possess both inhibitory activity will be very useful as active ingredients in the prevention and/or treatment of those diseases and disorders.

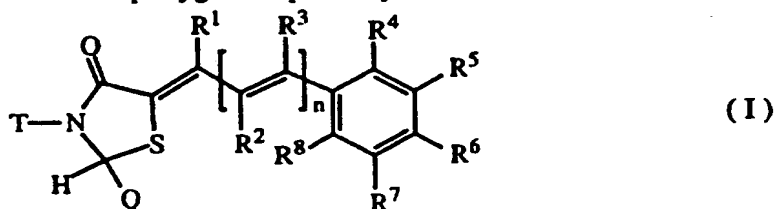
20 Accordingly, the present inventors have conducted long term investigations and studies on thiazolidin-4-one derivatives which have PAF antagonistic activity and/or leukotrienes inhibitory activity. The present invention has been accomplished based on these findings.

25 SUMMARY OF THE INVENTION

It is an object of this invention to provide novel thiazolidin-4-one derivatives which act as PAF antagonists and/or inhibit biosynthesis of leukotrienes via the 5-lipoxygenase pathway, the pharmaceutical uses of these derivatives, and a process for

preparing them.

The present invention relates to the novel thiazolidin-4-one derivatives having the following formula(I), which act as PAF antagonists and/or inhibit biosynthesis of leukotrienes via the 5-lipoxygenase pathway.

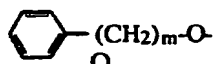


wherein, :

n is 0, 1, 2 or 3;

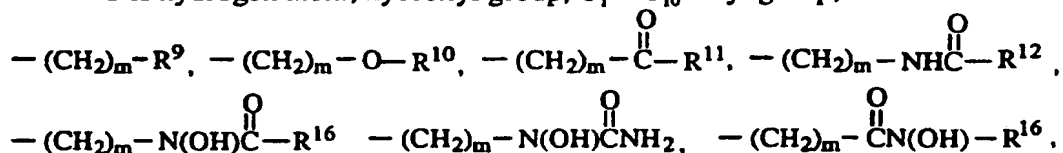
Q is $C_1 - C_{10}$ alkyl group, phenyl group that is optionally substituted with one or more suitable substituents selected from methoxy group and nitro group, or pyridyl group that is optionally substituted with one or more methyl group;

R^1 , R^2 and R^3 are independently hydrogen atom, $C_1 - C_{10}$ alkyl group, $C_3 - C_6$ cycloalkyl group, or phenyl group that is optionally substituted with one or more methoxy group;

R^4 , R^5 , R^6 , R^7 and R^8 are independently hydrogen atom, hydroxyl group, halogen atom, $C_1 - C_{10}$ alkyl group, $C_1 - C_{10}$ alkoxy group, nitro group, amino group that is optionally substituted with one or more suitable substituents selected from $C_1 - C_{10}$ alkyl group and $C_3 - C_6$ cycloalkyl group, phenyl group that is optionally substituted with one or more suitable substituents selected from methoxy group and nitro group, $C_1 - C_{10}$ haloalkyl group, , $(CH_2)_m-O$,

$-CO_2H$, $OCH_2OCH_2CH_2OCH_3$, $-OC(=O)R^{15}$, $-OCO(=O)R^{15}$, $-C(=O)R^{15}$, $-C(=O)NHR^{15}$, $-C(=O)OR^{15}$, $-NHC(=O)R^{15}$, $-CH_2NH-R^{15}$, $-N(OH)-C(=O)NHR^{15}$, $-C(=O)N(OH)R^{15}$, $-NHC(=O)N(OH)R^{15}$, $-CH_2NHC(=O)N(OH)R^{15}$, $-OC(=O)NR^{15}R^{15}$, $-OC(R^{16})_2-C(=O)OR^{15}$, $-OCH_2-O-C(=O)R^{15}$, $O-C(=O)-(CH_2)_m-C(=O)OH$, or $-O-C(=O)-(CH_2)_m-C(=O)OR^{15}$ (in which R^{15} is $C_1 - C_{10}$ alkyl group; m is 1, 2, 3 or 4); and

T is hydrogen atom, hydroxyl group, $C_1 \sim C_{10}$ alkyl group,



- 5 or $-(CH_2)_m-NR^{13}R^{14}$ (in which, m is 1, 2, 3 or 4; R^9 is hydrogen atom, phenyl group that is optionally substituted with one or more suitable substituents selected from $C_1 \sim C_6$ alkyl group and $C_1 \sim C_6$ alkoxy group, or a pyridyl group; R^{10} is hydrogen atom, $C_1 \sim C_{10}$ alkyl group, or $C_1 \sim C_4$ alkanoyl group; R^{11} is $C_1 \sim C_{10}$ alkyl group, $C_1 \sim C_{10}$ alkoxy group, or amino group that is optionally substituted with one or more
- 10 suitable substituents selected from $C_1 \sim C_{10}$ alkyl group and $C_3 \sim C_6$ cycloalkyl group; R^{12} is $C_1 \sim C_{10}$ alkyl group or phenyl group; R^{13} is hydrogen atom, $C_1 \sim C_{10}$ alkyl group, or $C_1 \sim C_{10}$ alkanoyl group; R^{14} is hydrogen atom or $C_1 \sim C_{10}$ alkyl group or when taken together, connecting R^{13} and R^{14} , a substituted or unsubstituted four- to seven-membered cycloamino group, or a cycloamino group
- 15 having another hetero atoms; and R^{16} is hydrogen atom or $C_1 \sim C_{10}$ alkyl group.

The present invention also includes pharmaceutically acceptable salts of the formula(I), including, for example, salts with mineral acids such as, e.g., hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid, or salts with organic carboxylic acid such as, e.g., formic acid, acetic acid, malic acid, citric acid, maleinic

20 acid, fumalic acid or tartaric acid.

And the compounds according to the invention, as well as the pharmaceutically acceptable salts thereof, may be existed geometrical or optical isomerism. Thus the present invention includes isomer in each case the isomerism and hydrate of the compounds.

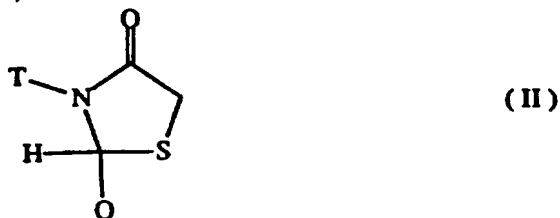
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DETAILED DESCRIPTION OF THE INVENTION

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory, and are intended to

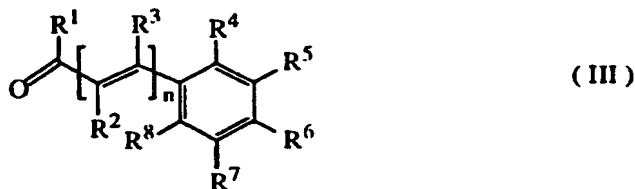
provide further explanation of the invention as claimed.

Novel compounds(I) of the present invention can be prepared by reacting compound of formula(II)



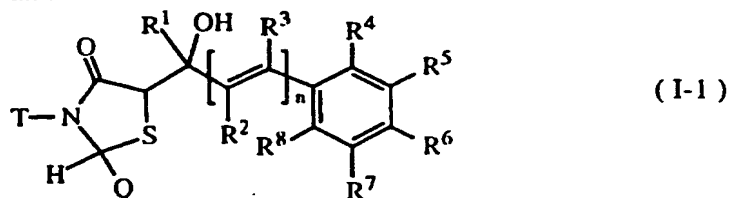
5 wherein, T and Q are defined as in the formula(I);

with compound of formula(III)



wherein, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are defined as in the formula(I);

10 in the presence of base and solvent at -78 °C to reflux temperature, via the formula (I-1) as an intermediate



wherein, n, T, Q, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are defined as in formula(I).

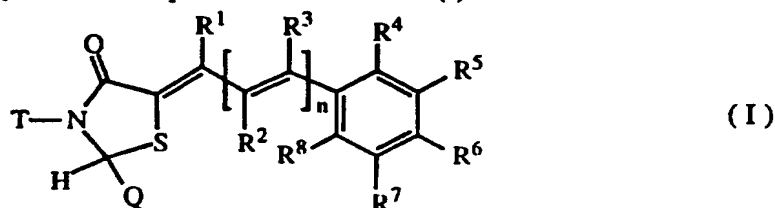
The reaction of compound(II) with compound(III) is preferably carried out in a suitable solvent which at least one selected from inert organic solvents such as, e.g., tetrahydrofuran, benzene, toluene, dichloromethane or dichloroethane, and polar organic solvents such as, e.g., methanol, ethanol, dimethylsulfoxide, *N,N*-dimethylformamide or acetic acid. The basic medium for the reaction of compound (II) and (III) is preferably metal hydride such as, e.g., sodium hydride, potassium hydride or calcium hydride, lithium diisopropylamide, methyl lithium, butyl lithium, phenyl lithium, sodium methoxide, sodium ethoxide, sodium acetate, sodium

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hydroxide, potassium hydroxide, or organic base such as, e.g., triethyl amine, piperidine or morpholine, etc..

Without isolation of the compound of formula(I-1) which is as an intermediate of the reaction mixtures, the reaction mixture can be reacted with an acid or alkali to immediately obtain compound of the formula(I).

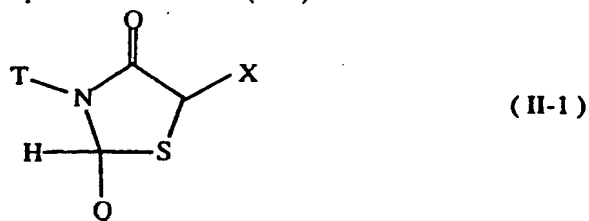


wherein, n, T, Q, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are defined as the above.

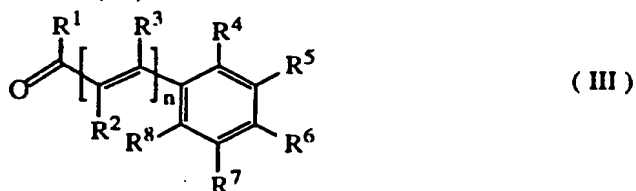
Suitable preferred acids are inorganic acid such as, e.g., hydrochloric acid, hydrochloric acid/methanol or hydrochloric acid/ethanol, or organic acid such as, e.g., acetic acid or *p*-toluenesulfonic acid, etc.. And suitable preferred alkalis are sodium hydroxide, potassium hydroxide, sodium methoxide or sodium ethoxide, etc..

If the reaction of compound(II) with compound(III) is carried out at -78 °C to 0 °C, the formula(I-1) as intermediate may be isolated from the reaction mixture in a high yield.

Also, according to the present invention the compound of formula(I) can be prepared by reacting compound of formula(II-1)

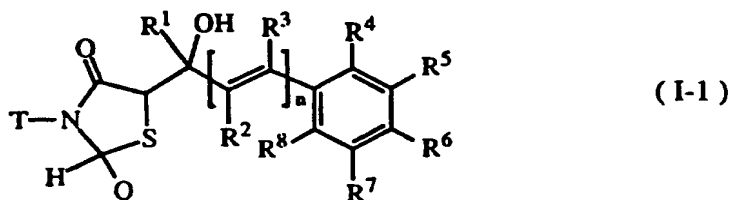


wherein, T and Q are defined as in the formula(I), and X is halogen atom; with compound of formula(III)



wherein, n , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are defined as in the formula(I);

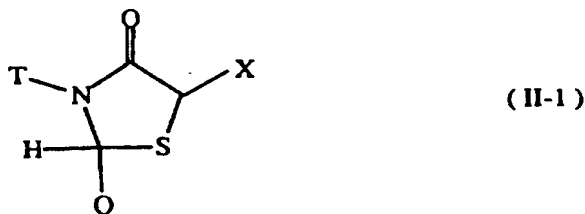
in the presence of zinc and an organic solvent in which tetrahydrofuran, benzene, toluene or trimethoxyborane at -78°C to reflux temperature, to obtain the formula (I-1) as intermediate



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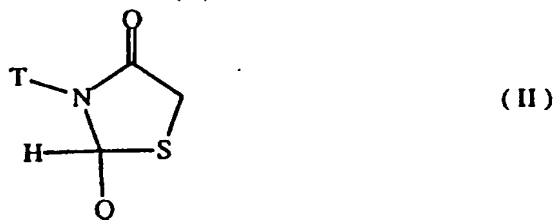
wherein, n , T , Q , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are defined as in the formula(I); and reacting the compound of formula(I-1) with the said acid or alkali.

Also, the present invention relates to process for preparing compound of formula(II-1)



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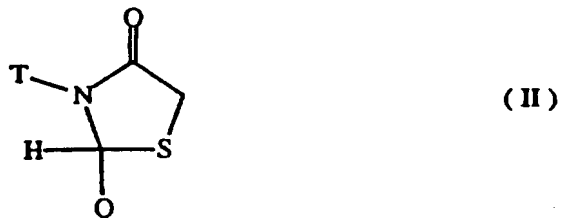
wherein, T and Q are as defined in formula(I), and X is halogen atom; reacting compound of formula(II)



wherein, T and Q are defined as in formula(I);

with halide such as, e.g., bromine, iodine, chlorine, *N*-bromosuccinimide, *N*-bromophthalimide, *N*-chlorosuccinimide or *N*-chlorophthalimide in an organic solvents such as, e.g., ether, tetrahydrofuran, chloroform, carbon tetrachloride, dichloromethane, benzene, toluene, dimethyl formamide or etc. at 0°C to reflux temperature.

Also, the present invention relates to process for preparing compound of formula(II)



wherein, T and Q are defined as in formula(I);

- 5 by dehydrating the compound of Q-CHO(wherein, Q is defined as in the formula(I)) with compound of T-NH₂(wherein, T is defined in the formula(I)) and mercaptoacetic acid(HSCH₂CO₂H) in an organic solvent such as, e.g., benzene, toluene, xylene and etc..

10 It is to be understood that application of the teaching of the present invention to a specific problem or environment will be within the capabilities of one having ordinary skill in the art in light of the teachings contained herein. Examples of the products of the present invention and a representative process for their preparation and recovery appear in the following examples.

EXAMPLE 1.

- 15 Preparation of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one

< Method A >

- A solution of 3-pyridinecarboxaldehyde(1.0 g, 9.15 mmol) and *N,N*-dimethylethylenediamine(0.822 g, 9.15 mmol) in toluene(30mL) was dehydrated under reflux for 1 h. The reaction mixture was allowed to cool to room temperature
20 and evaporated to give 1.63 g(100 %) of *N*-nicotinyldene-*N',N'*-dimethylethylenediamine.

¹H NMR(300 MHz, CDCl₃) δ : 8.86(d, J=2.4Hz, 1H), 8.64(dd, J=4.8Hz, Δν = 15Hz), 8.35(s, 1H), 8.11(m, 1H), 7.33(m, 1H), 3.78 (td, J=6.9, 1.2Hz, 2H), 2.68(t, J=6.9Hz, 2H), 2.34 (s, 6H).

To a stirred solution of *N*-nicotinyldene-*N',N'*-dimethylethylenediamine(1.63 g) in toluene(30mL) was added mercaptoacetic acid(0.64 mL, 9.15 mmol) and dehydrated at reflux for 1 h. The reaction mixture was allowed to cool to room temperature and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 2.14 g (93 %) of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one.

¹H NMR(300 MHz, CDCl₃) δ : 8.63(m, 1H), 8.56(d, *J*=2.1Hz, 1H), 7.68(m, 1H), 7.36(m, 1H), 5.93(s, 1H), 3.85~3.77(m, 3H), 2.74~2.69(m, 1H), 2.48~2.44(m, 1H), 2.29~2.21(m, 1H), 2.15(s, 6H).

< Method B >

A solution of 3-pyridinecarboxaldehyde(1.0 g, 9.15 mmol) and *N,N*-dimethylethylenediamine(0.822 g, 9.15 mmol) in toluene(30 mL) was dehydrated under reflux for 1 h. To reaction mixture was added mercaptoacetic acid(0.64 mL, 9.15 mmol) and dehydrated under reflux for 1 h. The reaction mixture was allowed to cool to room temperature and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 2.24 g(98 %)of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one.

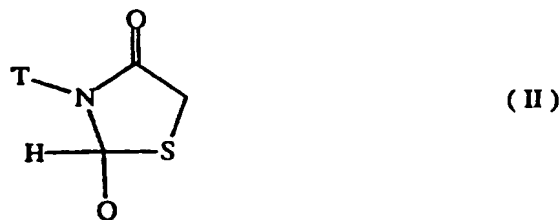
< Method C >

A solution of 3-pyridinecarboxaldehyde(1.0 g, 9.15 mmol), *N,N*-dimethylethylenediamine(0.822 g, 9.15 mmol) and mercaptoacetic acid(0.64 mL, 9.15 mmol) in toluene(50 mL) was dehydrated under reflux for 2 h. The reaction mixture was allowed to cool to room temperature and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 2.22 g(97 %) of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one.

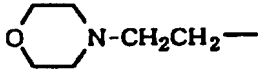
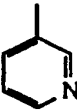
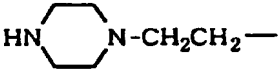
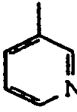
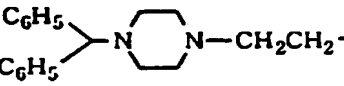
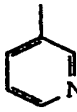
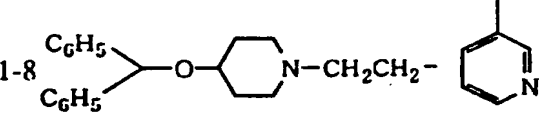
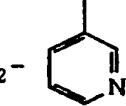
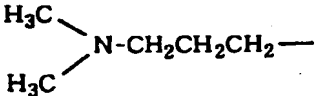
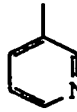
The intermediate compounds of formula(II) as shown in Table 1 were prepared in the same manner as described in EXAMPLE 1.

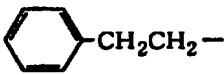
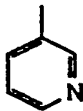
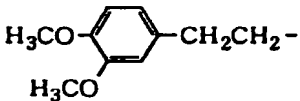
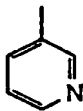
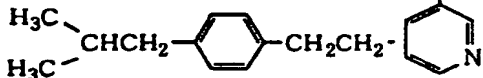
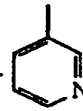
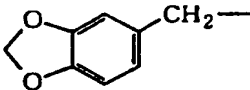
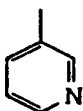
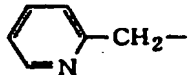
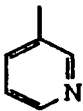
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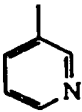
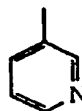
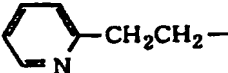
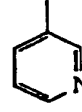
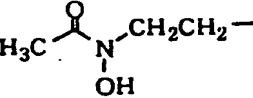
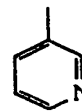
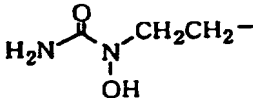
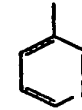
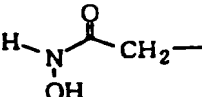
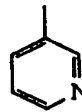
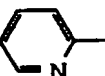
Table 1

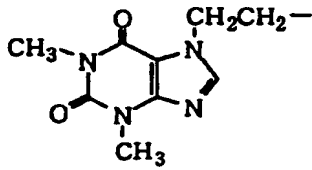
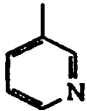
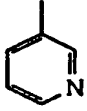
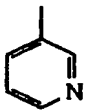
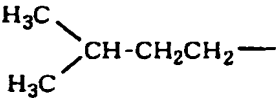
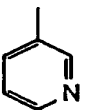
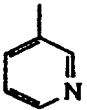
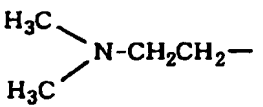


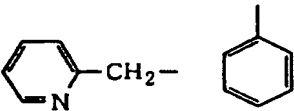
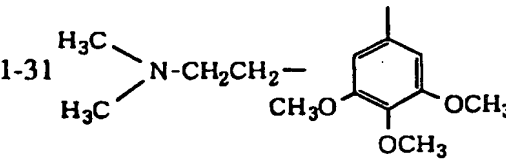
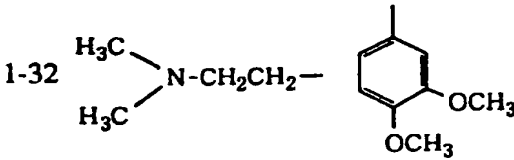
Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
5	1-1		8.63(m, 1H), 8.56(d, J=2.1Hz, 1H), 7.68(m, 1H), 7.36(m, 1H), 5.93(s, 1H), 3.85~3.77(m, 3H), 2.74~ 2.69(m, 1H), 2.48~2.44(m, 1H), 2.29~2.21(m, 1H), 2.15(s, 6H)
10	1-2		8.62(m, 1H), 8.55(m, 1H), 7.68(m, 1H), 7.38(m, 1H), 5.98(s, 1H), 3.65 ~3.85(m, 2H), 2.60~2.79(m, 2H), 2.33~2.57(m, 5H), 0.97(t, J=7.2Hz, 6H)
15	1-3		8.62(m, 1H), 8.60(m, 1H), 7.66(m, 1H), 7.35(m, 1H), 5.94(s, 1H), 3.84(m, 1H), 3.78(m, 2H), 2.74(m, 2H), 2.41(m, 5H), 1.74(m, 4H)
20	1-4		8.62(m, 1H), 8.55(m, 1H), 7.67(m, 1H), 7.35(m, 1H), 5.98(s, 1H), 3.72 ~3.88(m, 3H), 2.78(m, 1H), 2.51 (m, 1H), 2.29(m, 5H), 1.54(m, 4H), 1.42(m, 2H)

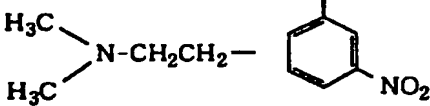
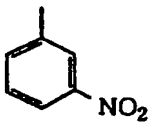
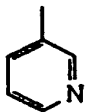
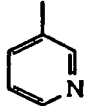
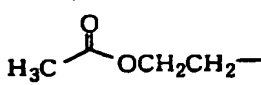
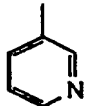
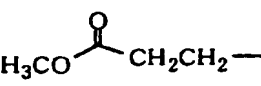
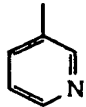
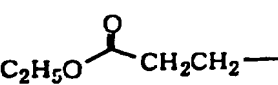
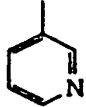
Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
1-5			8.63(m, 1H), 8.55(m, 1H), 7.68(m, 1H), 7.36(m, 1H), 5.89(s, 1H), 3.74~3.87(m, 3H), 3.67(m, 4H), 2.78(m, 1H), 2.48(m, 1H), 2.37(m, 5H)
1-6			8.63(m, 1H), 8.55(m, 1H), 7.68(m, 1H), 7.36(m, 1H), 5.92(s, 1H), 3.82(m, 1H), 3.78(m, 2H), 2.87(m, 4H), 2.77(m, 1H), 2.50(m, 1H), 2.35(m, 5H)
1-7			8.57(m, 1H), 8.52(m, 1H), 7.64(m, 1H), 7.10~7.44(m, 1H), 5.93(s, 1H), 4.21(s, 1H), 3.77(m, 3H), 2.73(m, 1H), 2.55(m, 1H), 2.39(m, 9H)
1-8			
1-9			8.63(m, 1H), 8.56(m, 1H), 7.67(m, 1H), 7.35(m, 1H), 5.71(s, 1H), 3.77(m, 2H), 3.68(m, 1H), 2.74(m, 1H), 2.24(m, 1H), 2.16(s, 6H), 1.70(m, 1H), 1.58(m, 1H)

Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
5	1-10		
			8.61(m, 1H), 8.53(m, 1H), 8.46(m, 1H), 7.64(m, 2H), 7.34(m, 1H), 7.19(m, 2H), 5.54(s, 1H), 4.02(m, 1H), 3.70(m, 2H), 2.80-3.20(m, 3H)
10	1-11		
			8.61(m, 1H), 8.41(m, 1H), 7.57(m, 1H), 7.33(m, 1H), 6.80(d, J=8.1Hz, 1H), 6.64 (m, 1H), 6.62(s, 1H), 5.25(s, 1H), 3.90 (m, 1H), 3.87(s, 3H), 3.85(s, 3H), 3.75 (m, 2H), 2.85(m, 2H), 2.68(m, 1H)
15	1-12		
			8.63(m, 1H), 8.44(d, J=1.8Hz, 1H), 7.64 (m, 1H), 7.34(m, 1H), 6.70(d, J=7.8Hz, 1H), 6.62(s, 1H), 6.45(d, J=7.8Hz, 1H), 5.95(s, 2H), 5.42(s, 1H), 4.25(ABq, Δ ν =467, J _{AB} = 15.0Hz, 2H), 3.84(ABq, Δν =40.0, J _{AB} = 15.6Hz, 2H)
20	1-13		
			8.60(m, 1H), 8.51(m, 1H), 7.60- 7.76(m, 2H), 7.34(m, 1H), 7.19(m, 1H), 5.83(s, 1H), 5.04(d, J _{gem} = 15.3Hz, 1H), 3.90 (m, 2H), 3.81(d, J _{gem} =15.3Hz, 1H)
25	1-14		
			8.60(m, 1H), 8.51(m, 1H), 7.60- 7.76(m, 2H), 7.34(m, 1H), 7.19(m, 1H), 5.83(s, 1H), 5.04(d, J _{gem} = 15.3Hz, 1H), 3.90 (m, 2H), 3.81(d, J _{gem} =15.3Hz, 1H)

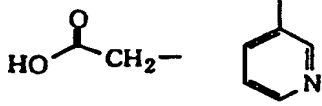
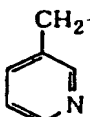
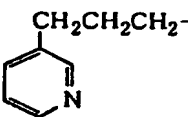
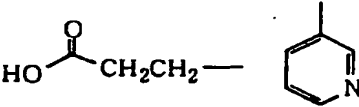
Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
5	1-15		
		<chem>CH3CH2CH2-O-</chem>	
	1-16		
			
10	1-17		
			
15	1-18		
			
20	1-19		8.63(m, 1H), 8.49(m, 1H), 7.34(m, 1H), 7.24(m, 1H), 5.89(s, 1H), 4.25(ABq, 2H), 3.98(ABq, 2H)
			
25	1-20		8.61(m, 1H), 8.46(m, 1H), 8.22(m, 1H), 8.10(d, J=8.4Hz, 1H), 7.67(m, 2H), 7.25 (m, 1H), 7.01(m, 1H), 6.87(s, 1H), 3.95 (ABq, Δν = 56.7Hz, J _{AB} =16.2Hz, 2H)
			

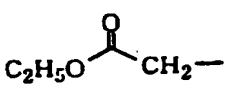
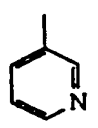
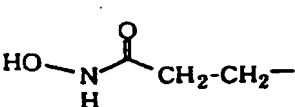
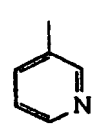
Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
5			8.52(m, 1H), 8.40(m, 1H), 7.52(m, 1H), 7.51(s, 1H), 7.18(m, 1H), 5.45 (s, 1H), 4.62(m, 1H), 4.37(m, 1H), 3.87(m, 1H), 3.80(dd, 2H), 3.60(s, 3H), 3.40(m, 1H), 3.34(s, 3H)
10	1-22 OH		8.57(s, 2H), 8.05(s, 1H), 7.78(d, J= 7.8Hz, 1H), 7.33(m, 2H), 5.79(s, 1H), 3.66(s, 2H)
15	1-23 CH ₃ -(CH ₂) ₃ -		8.64(m, 1H), 8.55(m, 1H), 7.68(m, 1H), 7.37(m, 1H), 5.65(d, J=1.5Hz, 1H), 3.70 (m, 1H), 2.64(m, 1H), 1.44(m, 2H), 1.27 (m, 2H), 0.87(t, J=7.5Hz, 3H)
20	1-24 		
	1-25 CH ₃ -		
25	1-26 	CH ₃ -(CH ₂) ₇ -	4.78(dd, J=6.3, 1.8Hz, 1H), 3.82(td, J= 7.2, 7.2Hz, 1H), 3.54(ABq, 2H), 3.07(td, J=7.2Hz, 2H), 2.35(m, 2H), 2.26(s, 6H), 1.92(m, 1H), 1.63(m, 1H), 1.18~1.46(m, 12H), 0.89(t, J=6.6Hz, 3H)

Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
5			4.57(m, 1H), 3.56(dd, 2H), 2.90(s, 3H),
	1-27	CH ₃ — CH ₃ -(CH ₂) ₇ —	1.84~1.99(m, 1H), 1.57~1.80 (m, 1H),
			1.05~1.55(m, 12H), 0.89(t, J=6.6Hz, 3H)
10			4.58(m, 1H), 3.57(ABq, 2H), 2.89 (s,
	1-28	CH ₃ — CH ₃ -(CH ₂) ₅ —	3H), 1.90(m, 1H), 1.72(m, 1H), 1.32(m,
			8H), 0.89(t, J=6.6Hz, 3H)
15			4.58(m, 1H), 3.54(ABq, Δν =28, JAB=
	1-29	CH ₃ — CH ₃ -(CH ₂) ₂ —	15.6Hz, 2H), 2.90(s, 3H), 1.83~1.99(m,
			1H), 1.61~1.79(m, 1H), 1.32~1.52(m,
20			2H), 0.98(t, J=7.2Hz, 3H)
	1-30		
	1-31		6.52(s, 2H), 5.80(s, 1H), 3.86(s, 9H), 3.79(m, 1H), 3.77(m, 2H), 2.86(m, 1H), 2.46(m, 1H), 2.34(m, 1H), 2.21(s, 6H)
25	1-32		

Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
1-33			
1-34	CH ₃ OCH ₂ CH ₂ -		
1-35	CH ₃ CH ₂ OCH ₂ CH ₂ -		
1-36			8.61(m, 2H), 7.68(m, 1H), 7.37(m, 1H), 5.81(d, J=0.9Hz, 1H), 3.76(m, 3H), 3.68 (s, 3H), 3.06(m, 1H), 3.71(m, 1H), 2.46 (m, 1H)
1-37			8.63(m, 2H), 7.70(m, 1H), 7.38(m, 1H), 5.81(s, 1H), 3.78(m, 3H), 3.67(s, 3H), 3.05(m, 1H), 2.71(m, 1H), 2.46(m, 1H)
1-38			8.61(m, 1H), 8.57(m, 1H), 7.82(m, 1H), 7.45(m, 1H), 5.90(d, J=1.2Hz, 1H), 4.02 (q, J=7.2Hz, 2H), 3.92 (dd, J=15.6, 1.2Hz, 1H), 3.67(d, J=15.6Hz, 1H), 3.61-3.73 (m, 1H), 2.87(m, 1H), 2.54(m, 1H), 2.40(m, 1H), 1.15(t, J=7.2Hz, 3H)

Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
1-39			
1-40			
1-41			
1-42			
1-43			
1-44			8.47(dd, J=4.8, 1.2Hz, 1H), 7.45 (dd, J=7.8, 1.5Hz, 1H), 7.21(m, 1H), 6.21(s, 1H), 3.85(td, J=7.8, 1.8Hz, 1H), 3.72(s, 2H), 2.72(m, 1H), 2.59(s, 3H), 2.52(m, 1H), 2.31(m, 1H), 2.13(s, 3H)
1-45			8.63(m, 1H), 8.56(d, J=2.1Hz, 1H), 7.68 (m, 1H), 7.36(m, 1H), 5.93(s, 1H), 3.85~3.77(m, 3H), 2.74~2.69 (m, 1H), 2.48~2.44(m, 1H), 2.15(s, 6H), 1.22(d, J=7.2Hz, 3H)
1-46			

Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
5	1-47		DMSO-d ₆ ; 8.60(d, J=1.8Hz, 1H), 8.55
			(dd, J=4.2, 1.8Hz, 1H), 7.85(m, 1H), 7.43(m, 1H), 5.85(s, 1H), 3.85 (ABq, Δν =72, J _{AB} =15.6Hz, 2H), 3.74(ABq, Δν =219, J _{AB} = 17.Hz, 2H)
10	1-48		8.53(m, 2H), 7.55(d, J=7.8Hz, 1H), 7.25
			m, 1H), 4.79(m, 1H), 3.17 (ABq, 2H), 3.04(s, 3H)
15	1-49		8.47(m, 2H), 7.50(m, 1H), 7.23(m, 1H), 4.60(dd, J=1.8, 5.1Hz), 3.55 (m, 2H), 2.86(s, 3H), 2.68(t, J= 5.7Hz, 2H), 1.62-1.98(m, 4H)
20	1-50		12.34(brs, 1H), 8.60(m, 1H), 8.58 (m, 1H), 7.83(m, 1H), 7.45(m, 1H), 5.91(d, J=1.2Hz, 1H), 3.92 (dd, J=15.6, 1.2Hz, 1H), 3.67(d, J=15.6Hz, 1H), 3.63(m, 1H), 2.83(m, 1H), 2.54(m, 1H), 2.29(m, 1H)

Example	T	Q	¹ H NMR(300 MHz, CDCl ₃) δ
5			8.61(m, 1H), 8.56(m, 1H), 7.86(m, 1H), 7.42(m, 1H), 5.86(s, 1H), 4.14(d, J=
1-51			17.4Hz, 1H), 4.02(d, J= 15.6Hz, 1H), 3.01(q, J=7.2Hz, 2H), 3.74(d, J=15.6Hz, 1H), 3.58(d, J= 17.4Hz, 1H), 1.13(t, J=
10			7.2Hz, 3H)
			10.51(s, 1H), 8.80(s, 1H), 8.59(m, 2H), 7.82(m, 1H), 7.46(m, 1H), 5.88(s, 1H), 3.93(d, J=15.3Hz, 1H), 3.63(m, 1H), 3.67(d, J=15.3Hz, 1H), 2.80(m, 1H), 2.29(m, 1H), 2.07(m, 1H)
1-52			
15			

EXAMPLE 2.

Preparation of 3-(2-dimethylaminoethyl)-5-(α -hydroxybenzyl)-2-(3-pyridyl)-thiazolidin-4-one

< Method A >

5 To a solution of diisopropylamine (0.142 mL, 0.796 mmol) in tetrahydrofuran (10 mL) was added *n*-BuLi (1.6 M solution, 0.5 mL, 0.80 mmol) at -78 °C. After stirred for 1 h. To the reaction mixture was added 3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one (0.20 g, 0.796 mmol) dissolved in tetrahydrofuran (1.5 mL). After stirred for 30 min, to the reaction mixture was added benzaldehyde (98 μ L, 0.950 mmol) and stirred for 1 h and allowed to warm to room temperature. The reaction mixture was poured into brine (2 mL) and it was then extracted by using ethyl acetate (30 mL).

The ethyl acetate phase was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 0.253 g (89 %) of 3-(2-dimethylaminoethyl)-5-(α -hydroxybenzyl)-2-(3-pyridyl)-thiazolidin-4-one.

^1H NMR (300 MHz, CDCl_3) δ : 8.62(m, 2H), 7.81(m, 1H), 7.36(m, 1H), 7.29~7.26(m, 5H), 5.84(s, 1H), 5.18(s, 1H), 4.52(s, 1H), 4.20(m, 1H), 2.75~2.35(m, 3H), 2.17(s, 6H).

20 **< Method B >**

To a solution of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one (0.35 g, 1.39 mmol) in carbon tetrachloride (30 mL) was added *N*-bromosuccinimide (0.260 g, 1.46 mmol) and benzoyl peroxide (1 mg). The reaction mixture was heated under reflux for 5 h in the dark and filtered off precipitate. The filtrate was evaporated to give crude 5-bromo-3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one.

^1H NMR (300 MHz, CDCl_3) δ : 8.62~8.58(m, 2H), 7.70(d, $J=8.1\text{Hz}$, 1H), 7.36~7.33(m, 1H), 5.94(s, 1H), 5.21(s, 1H), 4.68~4.80(m, 1H),

2.82(m, 1H), 2.61~2.43(m, 2H), 2.28(s, 6H).

To a solution of Zn(0.136 g, 2.09 mmol), CuBr(15 mg, 0.670 mmol) and diethylaluminium chloride (0.184 mg, 1.53 mmol) in mixture of tetrahydrofuran and hexane (10 mL/10 mL) was slowly added 5-bromo-3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one and benzaldehyde (0.162 g, 1.53 mmol) dissolved in tetrahydrofuran at -20 °C for 5 min. After stirred for 2 h, to the reaction mixture was added pyridine (1 mL) warmed to room temperature, diluted with water (10 mL) and extracted with ethyl acetate(80 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 0.468 g (94 %) of 3-(2-dimethylaminoethyl)-5-(α -hydroxybenzyl)-2-(3-pyridyl)-thiazolidin-4-one.

EXAMPLE 3.

Preparation of 3-(2-dimethylaminoethyl)-5-phenylmethylene-2-(3-pyridyl)-thiazolidin-4-one.

15 < Method A >

A solution of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one(0.130 g, 0.517 mmol) in tetrahydrofuran(10 mL) was cooled to 0 °C and added potassium hydride(51 mg, 1.29 mmol). After stirred for 5 min, to the reaction mixture was added benzaldehyde(64 μ l, 0.621 mmol) and warmed to room temperature. After stirred at room temperature for 1h, the reaction mixture was cooled to 0 °C, poured into water(0.2 mL), and extracted with ethyl acetate(20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 0.166 g (95 %) of 3-(2-dimethylaminoethyl)-5-phenylmethylene-2-(3-pyridyl)-thiazolidin-4-one.

^1H NMR(300 MHz, CDCl_3) δ : 8.65~8.61(m, 2H), 7.66(d, $J=8.1\text{Hz}$, 1H), 7.53(s, 1H), 7.44~7.34(m, 5H), 6.18(s, 1H), 4.08~3.97(m, 1H), 2.78~2.82(m, 1H), 2.63~2.53(m, 1H),

2.40~2.35(m, 1H), 2.19(s, 6H).

< Method B >

To a solution of 3-(2-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one (0.126 g, 0.501 mmol) in acetic acid(10 mL) was added sodium acetate (0.165 g, 20.1 mmol) and benzaldehyde(80 mg, 0.751 mmol). The reaction mixture was heated under reflux for 8 h and evaporated to dryness. The residue was dissolved in water(5 mL) and extrated with ethyl acetate(30 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 0.144 g (85 %) of 3-(2-dimethylaminoethyl)-5-phenylmethylene-2-(3-pyridyl)-thiazolidin-4-one.

< Method C >

To a solution of 3-(2-dimethylaminoethyl)-5-(α -hydroxybenzyl)-2-(3-pyridyl)-thiazolidin-4-one(0.20 g) in toluene(10 mL) was added *p*-toluenesulfonic acid(10 mg). The reaction mixture was dehydrated under reflux for 2 h, cooled to room temperature, and evaporated. The residue was purified by flash column chromatography on silica gel to give 0.188 g (99 %) of 3-(2-dimethylaminoethyl)-5-phenylmethylene-2-(3-pyridyl)-thiazolidin-4-one.

< Method D >

A solution of 3-(2-dimethylaminoethyl)-5-(α -hydroxybenzyl)-2-(3-pyridyl)-thiazolidin-4-one(0.40 g) dissolved in 28 % HCl-ethanol (5 mL) was stirred for 10 min at room temperature and evaporated. The residue was purified by flash column chromatography on silica gel to give 0.345 g (91 %) of 3-(2-dimethylaminoethyl)-5-phenylmethylene-2-(3-pyridyl)-thiazolidin-4-one.

EXAMPLE 4.

Preparation of 3-(2-dimethylaminoethyl)-5-phenylmethylene-2-(3-pyridyl)-thiazolidin-4-one hydrochloride salt (Compound No. 1).

A solution of 3-(2-dimethylaminoethyl)-5-phenylmethylene-2-(3-pyridyl)-thiazolidin-4-one (0.50g) dissolved in 28 % HCl-ethanol (2 mL) was stirred for 3 h at room

temperature and filtered the precipitate. The precipitate was dried under vac. to give 0.537 g(97 %) of 3-(2-dimethylaminoethyl)-5-phenylmethylene-2-(3-pyridyl)-thiazolidin-4-one hydrochloride salt.

¹H NMR(300 MHz, DMSO-d₆) δ : 9.70(s, 1H), 8.79(s, 1H), 8.69(d, J=4.5Hz, 1H),
5 7.97(d, J=8.1Hz, 1H), 7.60~7.55(m, 6H), 6.39(s, 1H), 4.20~4.12(m, 1H), 3.21~3.00(m, 3H), 2.82(d, J=3.9Hz, 6H).

The compounds of formula(I), wherein R⁴, R⁵, R⁶, R⁷ or R⁸ is an hydroxyl group, can be prepared in the following EXAMPLE 5, introducing protecting group
10 such as methoxyethoxymethyl group.

EXAMPLE 5.

Preparation of 3-(2-N, N-dimethylaminoethyl)-5-(3,5-dimethyl-4-hydroxy-phenylmethylene)-2-(3-pyridyl)-thiazolidin-4-one hydrochloride salt (Compound No. 10)

15 A solution of 3,5-dimethyl-4-hydroxybenzaldehyde (10.0 g, 66.6 mmol) in tetrahydrofuran(100 mL) was cooled to 0 °C and added 80 % NaH (2.40 g, 79.9 mmol). After stirred for 10 min at 0 °C, to the reaction mixture was added 2-methoxyethoxymethyl chloride (11.6 g, 93.2 mmol) and warmed to room temperature. After stirred for 4 h, the reaction mixture was cooled to 0 °C and added methanol (10
20 mL). When no more evolution of hydrogen gas the reaction mixture was warmed to room temperature added water(20 mL) and extracted with ethyl acetate(2 x 100 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 13.6 g(86%) of 3,5-dimethyl-4-(2-
25 methoxyethoxymethoxy)-benzaldehyde.

¹H NMR(300 MHz, CDCl₃) δ : 9.87(s, 1H), 7.55(s, 2H), 5.12(s, 2H), 3.95(t, J=4.5Hz, 2H), 3.60(t, J=4.5Hz, 2H), 3.39(s, 3H), 2.35
(s, 6H)

To a solution of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one (1.00 g, 3.98 mmol) in tetrahydrofuran(50 mL) was added lithium diisopropylamide (1.5M solution, 3.18 mL) at -78 °C and stirred for 10 min. To the reaction mixture was slowly added 3,5-dimethyl-4-(2-methoxyethoxymethoxy)-benzaldehyde(1.13 g, 4.77 mmol) dissolved in tetrahydrofuran(5 mL). After stirred at -78 °C for 2 h, to the reaction mixture was added acetic acid(2 mL) and warmed to room temperature. The reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate(3 x 30 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was dissolved in 30% HCl-ethanol solution(5 mL), stirred for 3 h and then neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (2 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 1.32 g(87 %) of 3-(2-*N,N*-dimethylaminoethyl)-5-(3,5-dimethyl-4-hydroxy-phenylethylene)-2-(3-pyridyl)-thiazolidin-4-one.

¹H NMR(300 MHz, CDCl₃) δ : 8.63~8.61(m, 2H), 7.75(m, 1H), 7.54(s, 1H), 7.35(m, 1H), 7.21(s, 2H), 6.17(s, 1H), 4.15(m, 1H), 2.85(m, 1H), 2.60(m, 1H), 2.38(m, 1H), 2.18(s, 6H)

To a solution of 3-(2-*N,N*-dimethylaminoethyl)-5-(3,5-dimethyl-4-hydroxy-phenylethylene)-2-(3-pyridyl)-thiazolidin-4-one(1.32 g, 3.44 mmol) in ethanol(4 mL) was added 30 % HCl-ethanol solution(0.94 mL) and stirred at room temperature for 30 min. To the reaction mixture was added ethyl acetate(30 mL), filtered, and dried to give 1.49 g(95 %) of 3-(2-*N,N*-dimethylaminoethyl)-5-(3,5-dimethyl-4-hydroxy-phenylethylene)-2-(3-pyridyl)-thiazolidin-4-one hydrochloride salt.

¹H NMR(300 MHz, DMSO-d₆) δ : 9.60(brs, 1H), 8.80(s, 1H), 8.68(d, *J*=4.5Hz, 1H), 8.01(m, 1H), 7.61(m, 1H), 7.38(s, 1H), 7.16(s, 2H), 6.26(s, 1H), 4.20(m, 1H), 3.31~3.01(m, 3H), 2.82(d,

$J=3.8\text{Hz}$, 6H), 2.36(s, 6H)

The thiazolidin-4-one derivatives of formula(I) as shown in Table 2 were prepared in the same manner as described in EXAMPLE 1 to EXAMPLE 5.

5

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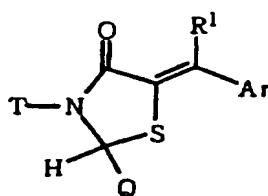
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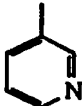
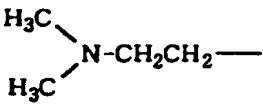
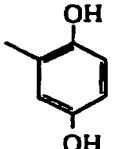

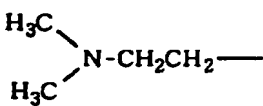
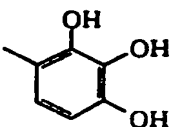
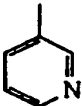
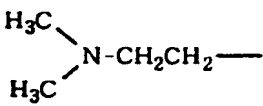
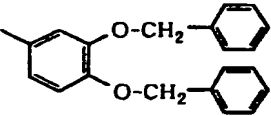
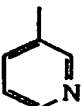
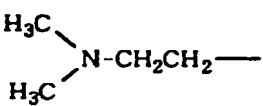
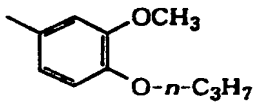
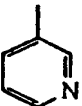
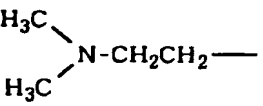
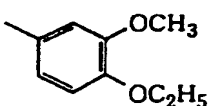

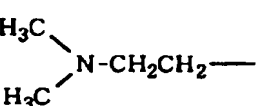
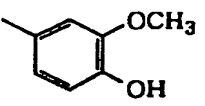

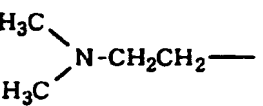
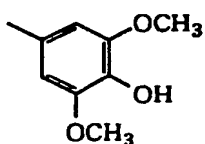
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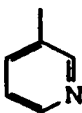
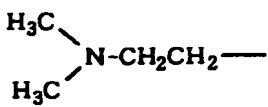
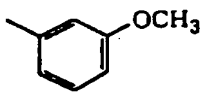
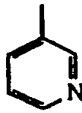
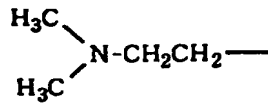
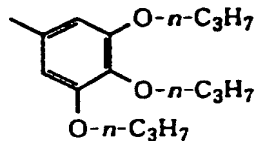
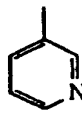
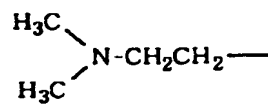
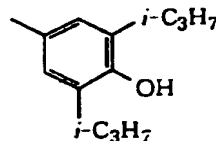
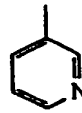
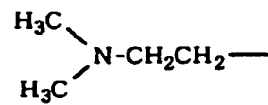
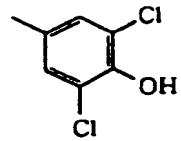
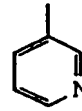
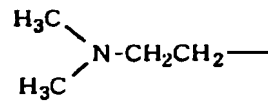
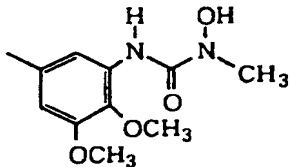
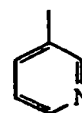
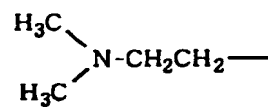
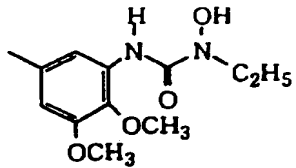
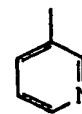
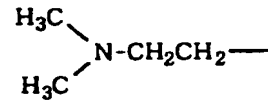
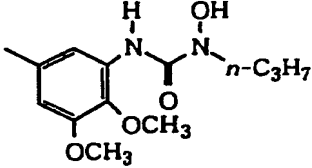
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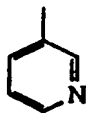
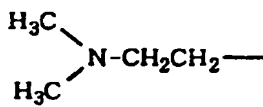
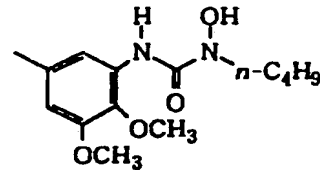

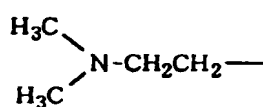
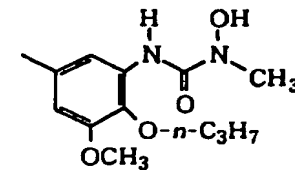
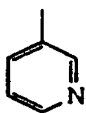
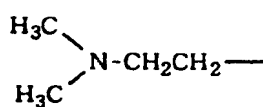
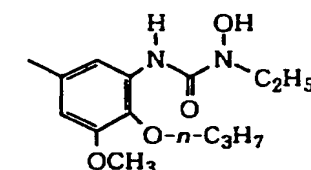
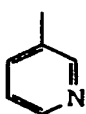
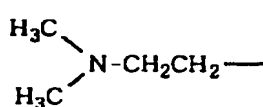
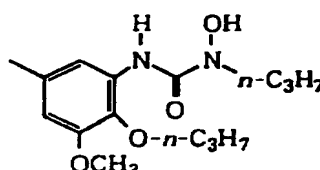
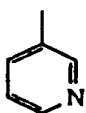
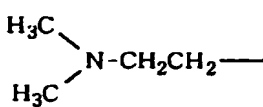
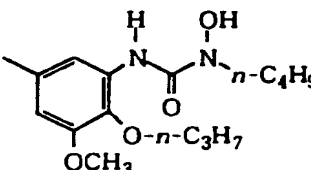
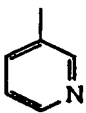
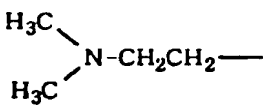
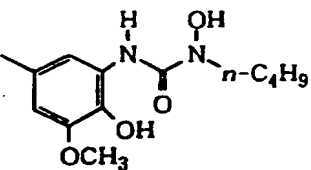
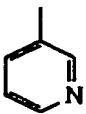
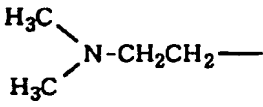
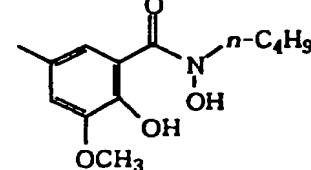


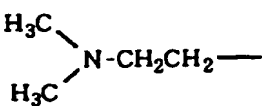
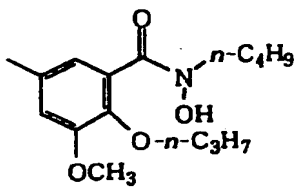
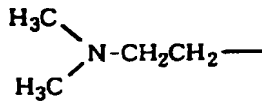
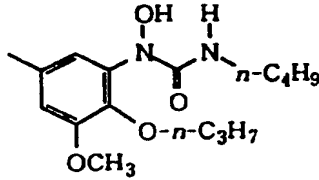
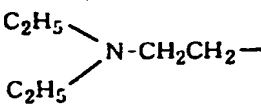
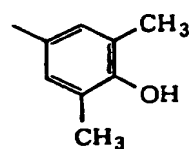
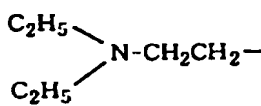
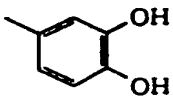
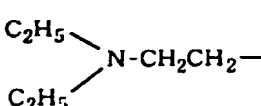
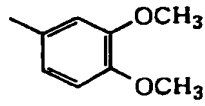
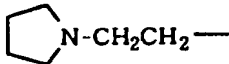
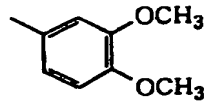
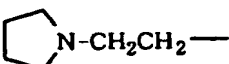
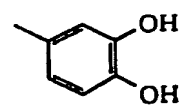
5	Comp. No.	Q	T	R ¹	Ar	Salt
	1			H		HCl
10	2			H		
	3			H		
15	4			H		HCl
20	5			H		HCl
	6			H		HCl
25	7			H		

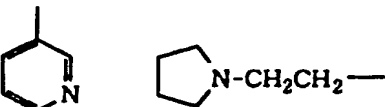
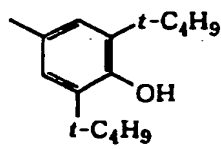
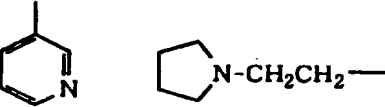
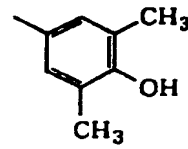
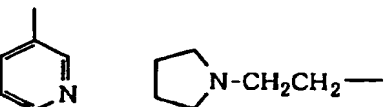
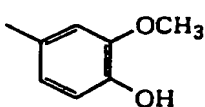
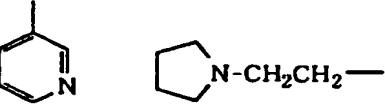
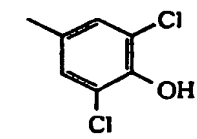
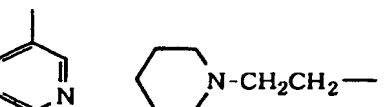
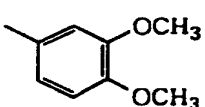
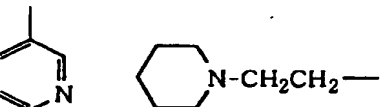
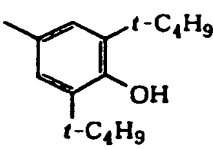
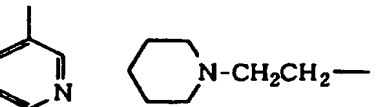
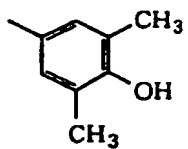
Comp. No.	Q	T	R ¹	Ar	Salt
5	8		H		
	9		H		HCl
	10		H		HCl
	11		H		
	12		H		
20	13		H		
	14		H		HCl


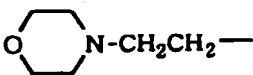
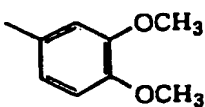
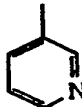
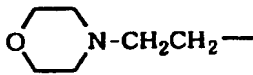
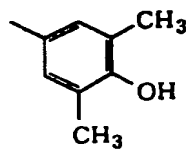
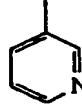
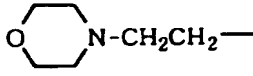
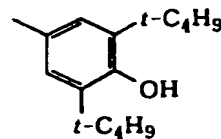
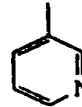
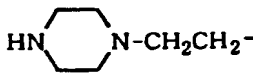
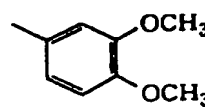
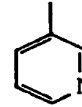
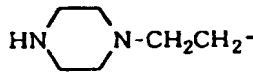
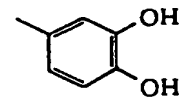
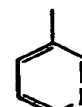
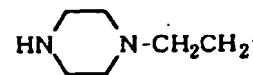
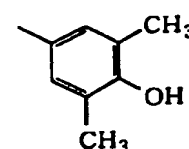
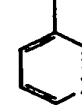
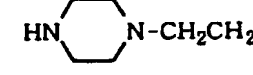
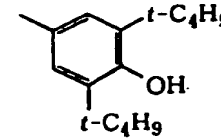
	Comp. No.	Q	T	R ¹	Ar	Salt
5	15			H		HCl
	16			H		HCl
10	17			H		
15	18			H		HCl
	19			H		
20	20			H		HCl
25	21			H		HCl

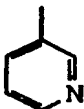
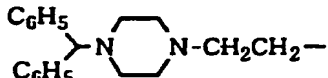
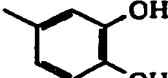
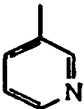
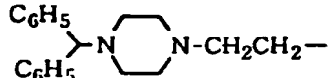
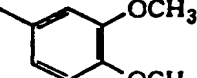
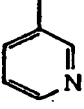
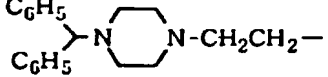
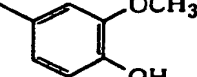
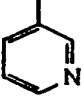
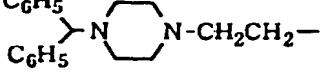
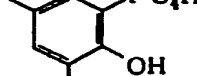
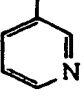
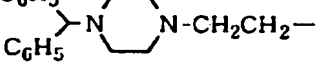
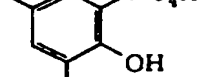
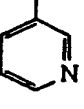
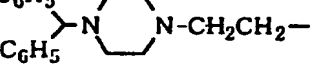
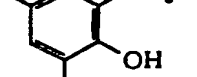
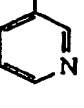
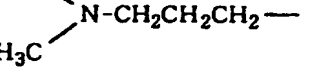
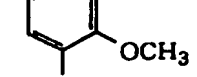
	Comp. No.	Q	T	R ¹	Ar	Salt
5	22			H		HCl
	23			H		HCl
10	24			H		
15	25			H		
	26			H		
20	27			H		
25	28			H		

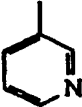
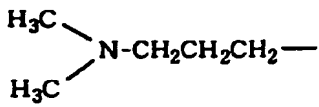
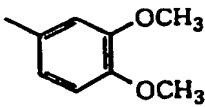
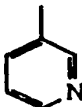
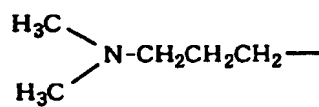
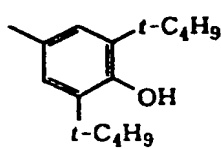
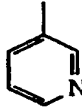
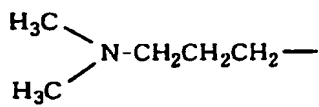
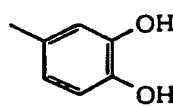
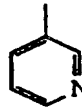
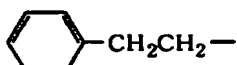
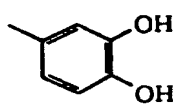
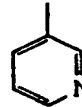
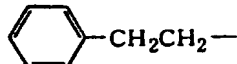
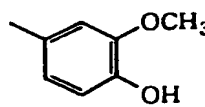
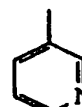
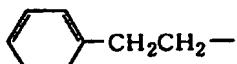
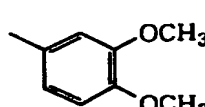
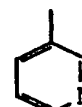
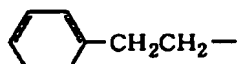
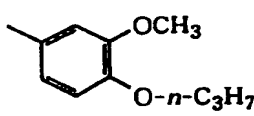
Comp. No.	Q	T	R ¹	Ar	Salt	
5	29			H		
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20	34			H		
	35			H		
25						

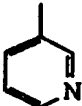
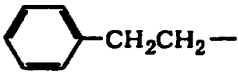
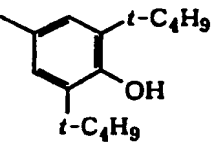
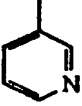
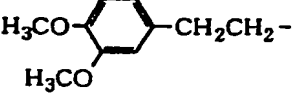
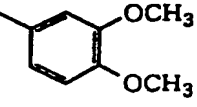
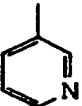
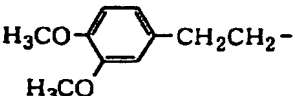
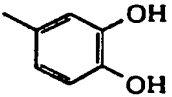
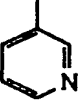
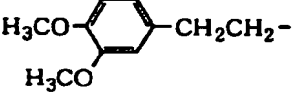
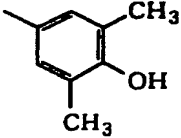
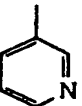
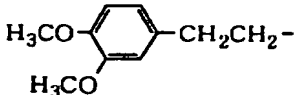
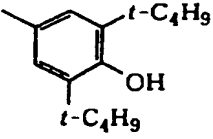
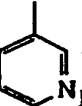
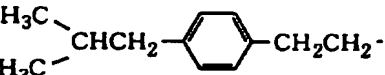
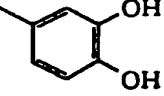
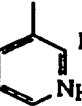
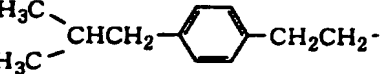
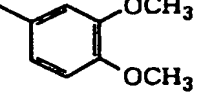
Comp. No.	Q	T	R ¹	Ar	Salt
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15	39		H		HCl
	40		H		
20	41		H		
25	42		H		

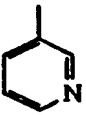
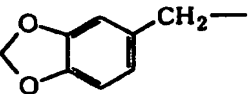
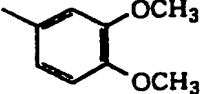
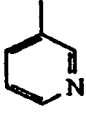
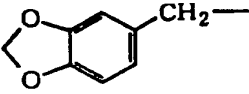
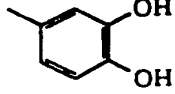
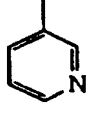
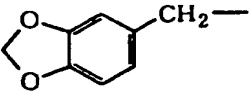
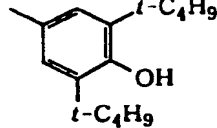
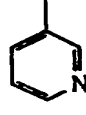
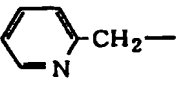
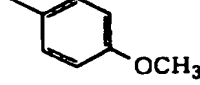
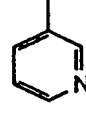
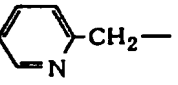
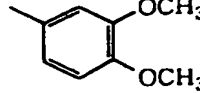
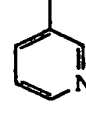
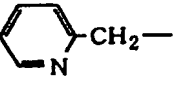
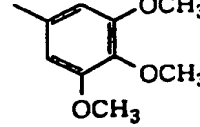
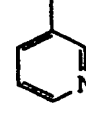
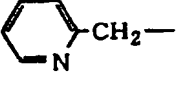
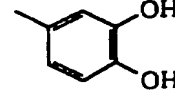
Comp. No.	Q	T	R ¹	Ar	Salt
5	43		H		
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10	45		H		
	46		H		
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20	48		H		
	49		H		
25					

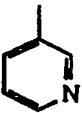
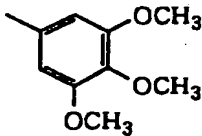
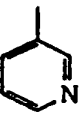
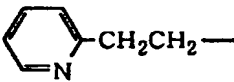
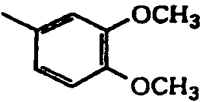
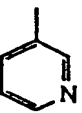
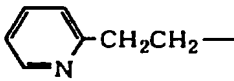
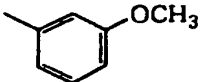
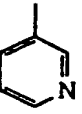
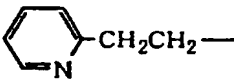
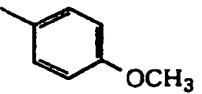
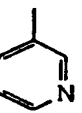
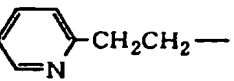
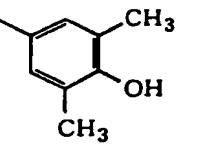
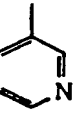
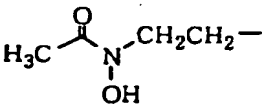
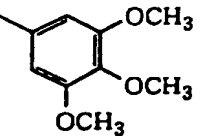
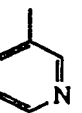
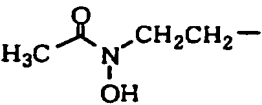
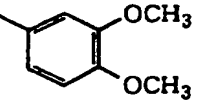
Comp. No.	Q	T	R ¹	Ar	Salt
5			H		
10			H		
15			H		
20			H		
25			H		
			H		
			H		

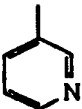
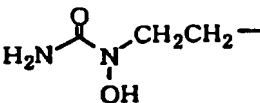
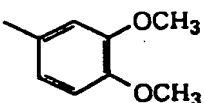
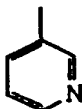
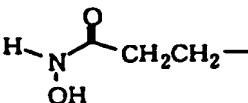
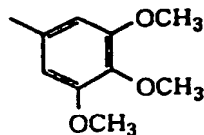
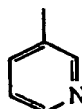
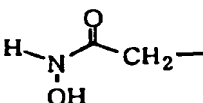
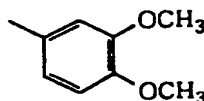
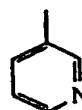
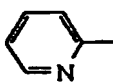
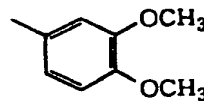
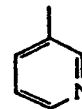
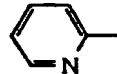
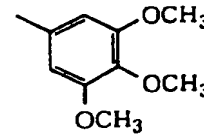
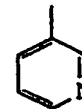
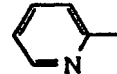
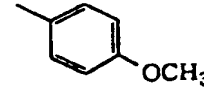
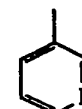
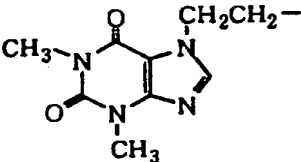
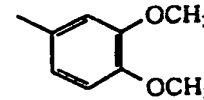
Comp. No.	Q	T	R ¹	Ar	Salt	
5	57			H		
	58			H		
10	59			H		
15	60			H		
	61			H		
20	62			H		
25	63			H		HCl

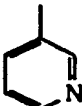
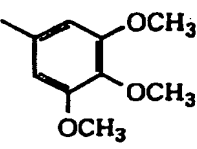
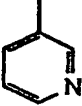
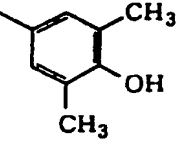
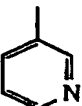
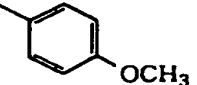
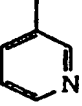
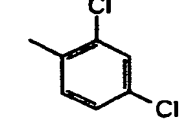
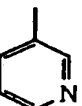
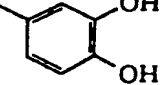
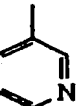
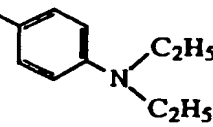
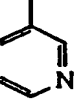
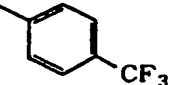
	Comp. No.	Q	T	R ¹	Ar	Salt
5	64			H		HCl
	65			H		
	66			H		
15	67			H		HCl
	68			H		HCl
20	69			H		HCl
	70			H		HCl

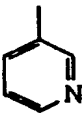
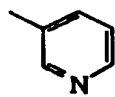
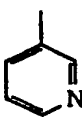
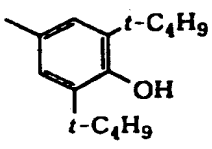
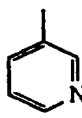
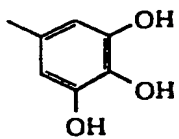
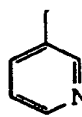
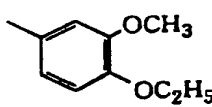
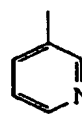
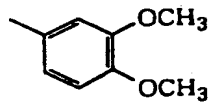
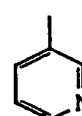
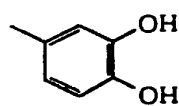

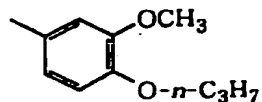
Comp. No.	Q	T	R ¹	Ar	Salt
5	71			H	 HCl
	72			H	
10	73			H	 HCl
15	74			H	
	75			H	
20	76			H	
	77			H	


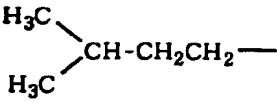
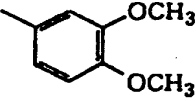
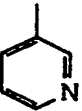
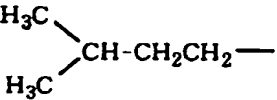
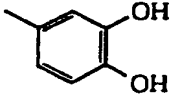
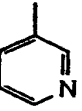
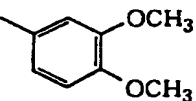
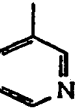
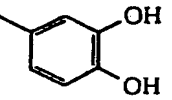
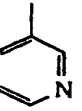
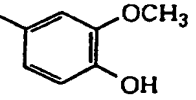
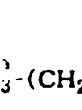
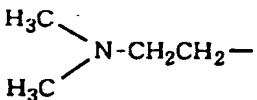
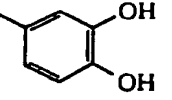
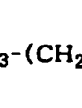
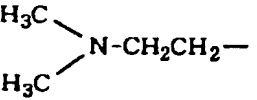
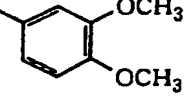
	Comp. No.	Q	T	R ¹	Ar	Salt
5	78			H		
	79			H		HCl
10	80			H		HCl
15	81			H		
	82			H		
20	83			H		
25	84			H		HCl

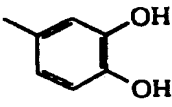
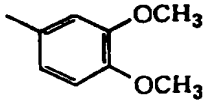
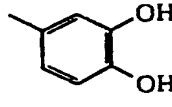
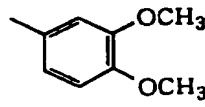
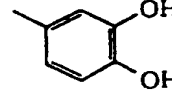
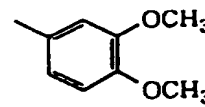
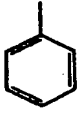
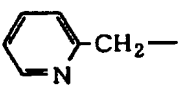
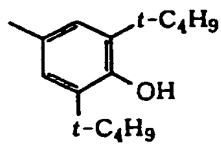
Comp. No.	Q	T	R ¹	Ar	Salt
5		$\text{CH}_3\text{CH}_2\text{CH}_2\text{-O-}$	H		HCl
			H		
10			H		
			H		
15			H		HCl
20			H		
			H		HCl
25					

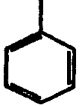
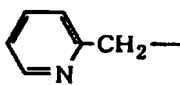
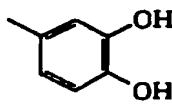
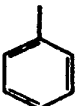
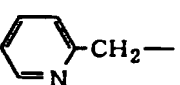
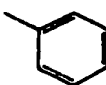
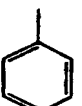
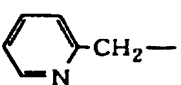
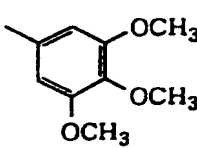
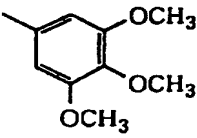
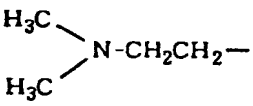
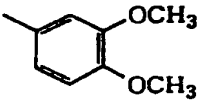
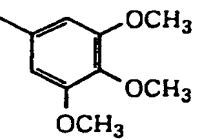
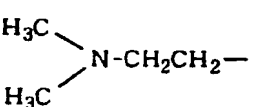
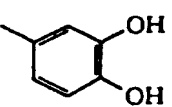
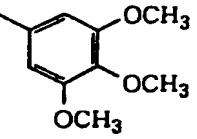
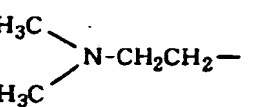
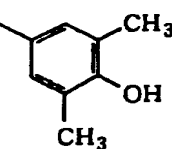
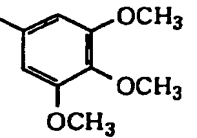
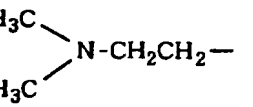
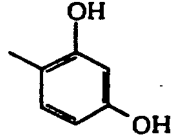
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	93			H		HCl
	94			H		
10	95			H		
15	96			H		
	97			H		
20	98			H		

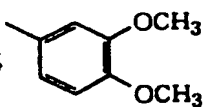
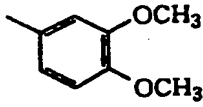
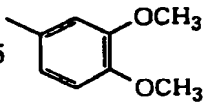
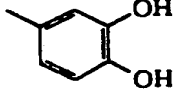
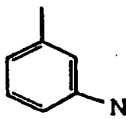
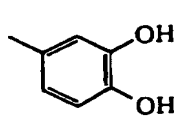
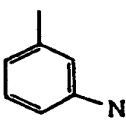
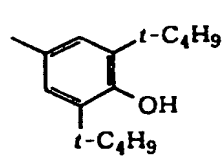
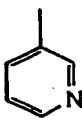
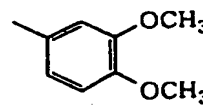
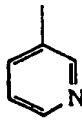
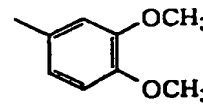
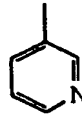
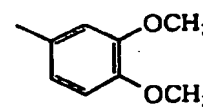
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	100		OH	H		HCl
10	101		OH	H		
	102		OH	H		HCl
15	103		OH	H		HCl
	104		OH	H		HCl
20	105		OH	H		
25						


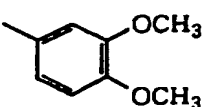

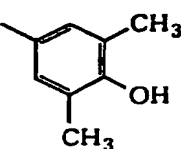

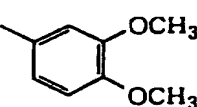
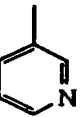

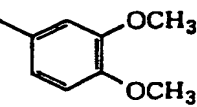
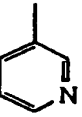
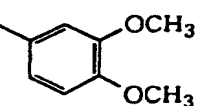
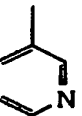

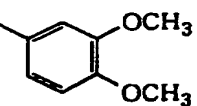
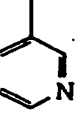

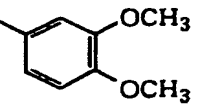
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	107		OH	H		
10	108		OH	H		HCl
15	109		CH ₃ -(CH ₂) ₃ —	H		
	110		CH ₃ -(CH ₂) ₃ —	H		HCl
20	111		CH ₃ -(CH ₂) ₃ —	H		HCl
	112		CH ₃ -(CH ₂) ₃ —	H		

Comp. No.	Q	T	R ¹	Ar	Salt
5	113			H	
	114			H	
10	115		CH ₃ -	H	
	116		CH ₃ -	H	
15	117		CH ₃ -	H	
	118			H	
20	119			H	

	Comp. No.	Q	T	R ¹	Ar	Salt
5	120	CH ₃ -(CH ₂) ₇ —	CH ₃ -	H		
	121	CH ₃ -(CH ₂) ₇ —	CH ₃ -	H		
10	122	CH ₃ -(CH ₂) ₅ —	CH ₃ -	H		
	123	CH ₃ -(CH ₂) ₅ —	CH ₃ -	H		
15	124	CH ₃ -(CH ₂) ₂ —	CH ₃ -	H		
20	125	CH ₃ -(CH ₂) ₂ —	CH ₃ -	H		
25	126			H		HCl

	Comp. No.	Q	T	R ¹	Ar	Salt
5	127			H		
	128			H		
10	129			H		
15	130			H		
	131			H		HCl
20	132			H		HCl
25	133			H		HCl

	Comp. No.	Q	T	R ¹	Ar	Salt
5	134		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{-}$	H		
	135		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{-}$	H		
10	136		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{-}$	H		
	137		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{-}$	H		
15	138		$\text{CH}_3\text{OCH}_2\text{CH}_2\text{-}$	H		
	139		$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{-}$	H		
20	140		$\text{H}_3\text{C-C(=O)-OCH}_2\text{CH}_2\text{-}$	H		
25						

Comp. No.	Q	T	R ¹	Ar	Salt
5	141		$\text{CH}_3\text{CH}_2\text{O}-\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-$	H	
	142		$\text{C}_2\text{H}_5\text{O}-\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-$	H	
10	143		$\text{H}_3\text{C}-\text{C}(=\text{O})-\text{N}(\text{H})-\text{CH}_2\text{CH}_2-$	H	
15	144		 - $\text{C}(=\text{O})-\text{N}(\text{H})-\text{CH}_2\text{CH}_2-$	H	
	145		$\text{H}_3\text{C}-\text{N}(\text{CH}_3)-\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-$	H	
20	146		 - $\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-$	H	
25	147		 - $\text{C}(=\text{O})-\text{CH}_2\text{CH}_2-$	H	

EXAMPLE 6.

Preparation of 3-(2-*N, N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(4-hydroxy-3-methoxyphenylallyliden)-thiazolidine-4-one hydrochloride salt(Compound No. 148)

A solution of 4-hydroxy-3-methoxy-cinnamaldehyde(2.0 g, 11.2 mmol) in
5 tetrahydrofuran(20 mL) was cooled to 0 °C and added 80 % NaH(0.404 g, 13.5 mmol).

After stirred for 10 min at 0 °C, to the reaction mixture was added 2-methoxyethoxymethyl chloride (1.68 g, 13.5 mmol) and warmed to room temperature.

After stirred for 3 h, the reaction mixture was cooled to 0 °C and added methanol(4 mL). When no more evolution of hydrogen gas the reaction mixture was warmed to
10 room temperature added water(10 mL), and extracted with ethyl acetate(2 x 50 mL).

The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 2.74 g(92 %) of 3-methoxy-4-(2-methoxyethoxymethoxy)-cinnamaldehyde.

15 ¹H NMR(300 MHz, CDCl₃) δ : 9.66(d, *J*=7.8Hz, 1H), 7.42(d, *J*=15.9Hz, 1H), 7.24
(d, *J*=8.4Hz, 1H), 7.13(dd, *J*=8.4, 2.1Hz, 1H), 7.09
(d, *J*=2.1Hz, 1H), 6.62(dd, *J*=15.9, 7.8Hz, 1H),
5.38(s, 2H), 3.89(s, 3H), 3.85(m, 2H), 3.55(m, 2H),
3.37(s, 3H)

20 To a solution of 3-(2-*N, N*-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one
(1.00g, 3.98 mmol) in tetrahydrofuran(30 mL) was added lithium diisopropylamide
(1.5M solution, 3.18 mL) at -78 °C and stirred for 10 min. To the reaction mixture
was slowly added 3-methoxy-4-(2-methoxyethoxymethoxy)-cinnamaldehyde(1.27 g,
4.77 mmol) dissolved in tetrahydrofuran(5 mL). After stirred at -78 °C for 3 h, the
25 reaction mixture was added acetic acid(4 mL) and allowed to warm to room
temperature. The reaction mixture was neutralized with saturated sodium
bicarbonate solution and extracted with ethyl acetate(2 x 50 mL). The combined
organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to

dryness. The residue was dissolved in 30% HCl-ethanol solution(10 mL) stirred at room temperature for 3h and then neutralized with saturated sodium bicarbonate solution, extracted with ethyl acetate(2 x 50 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to give pale yellow solids. The residue was purified by flash column chromatography on silica gel to give 1.35 g (83 %) of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(4-hydroxy-3-methoxyphenylallylidene) thiazolidin-4-one.

¹H NMR(300 MHz, CDCl₃) δ : 8.62(m, 2H), 7.65(m, 1H), 7.38(m, 1H), 7.23(d, *J*=11.1Hz, 1H), 6.98(d, *J*=8.4Hz, 1H), 6.92(s, 1H), 6.85(d, *J*=8.4Hz, 1H), 6.75(d, *J*=15.3Hz, 1H), 6.58(dd, *J*=15.3, 11.1Hz, 1H), 6.15(s, 1H), 3.92(m, 1H), 3.91(s, 3H), 2.83(m, 1H), 2.59(m, 1H), 2.28(m, 1H), 2.20(s, 6H)

To a solution of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(4-hydroxy-3-methoxyphenylallylidene)thiazolidin-4-one(1.35 g, 3.28 mmol) in ethanol(4 mL) was added 30 % HCl-ethanol solution(0.98 mL) and stirred at room temperature for 1 h. To the reaction mixture was added ethyl acetate(30 mL), filtered, and evaporated to give 1.53 g(97 %) of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(4-hydroxy-3-methoxyphenylallylidene)-thiazolidine-4-one hydrochloride salt.

20 EXAMPLE 7.

Preparation of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(3,5-dimethyl-4-hydroxyphenylallylidene)-thiazolidine-4-one (Compound No. 150)

A solution of 3,5-dimethyl-4-hydroxycinnamaldehyde(2.0 g, 11.4 mmol) in tetrahydrofuran(25 mL) was cooled to 0 °C and added 80 % NaH(0.425 g, 14.2 mmol). After stirred for 15 min, at 0 °C, to the reaction mixture was added 2-methoxyethoxymethyl chloride(2.12 g, 17.0 mmol) and warmed to room temperature. After stirred for 4 h, the reaction mixture was cooled to 0 °C, added methanol(10 mL) and then warmed to room temperature, added water(20 mL), and extracted with ethyl

acetate(2 x 40 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 2.34 g(78 %) of 3,5-dimethyl-4-(2-methoxyethoxymethoxy)-cinnamaldehyde.

- 5 $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 9.65(d, $J=7.8\text{Hz}$, 1H), 7.36(d, $J=15.6\text{Hz}$, 1H), 7.24 (s, 2H), 6.02(dd, $J=15.6$, 7.8Hz, 1H), 5.09(s, 2H), 3.95(m, 2H), 3.62(m, 2H), 3.40(s, 3H), 2.31(s, 6H)

- To a solution of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-thiazolidin-4-one (0.193g, 0.768 mmol) in tetrahydrofuran(8 mL) was added lithium diisopropylamide (1.5M solution, 1.0 mL) at -78 °C and stirred for 5 min. To the reaction mixture was slowly added 3,5-dimethyl-4-(2-methoxyethoxymethoxy)-cinnamaldehyde(0.225 g, 0.683 mmol) dissolved in tetrahydrofuran(1 mL). After stirred at -35 °C ~ -40 °C for 1 h, the reaction mixture was added acetic acid(1mL), allowed to warm to room temperature, and evaporated. To the residue was added 30 % HCl-ethanol solution(5 mL), stirred at room temperature for 2 h and it was then neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate(2 x 25 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 0.14 g (45 %) of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(3,5-dimethyl-4-hydroxyphenylallylidene)-thiazolidine-4-one.
- 10
15
20

- $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 8.64~8.59(m, 2H), 7.69~7.66(m, 1H), 7.37~7.33(m, 1H), 7.22(d, $J=11.1\text{Hz}$, 1H), 7.09(s, 2H), 6.72(d, $J=15.3\text{Hz}$, 1H), 6.55(dd, $J=15.3$, 11.1Hz, 3.98~3.90 (m, 1H), 2.86~2.77(m, 1H), 2.60~2.51(m, 1H), 2.37~2.28(m, 1H), 2.24(s, 6H), 2.18(s, 6H)
- 25

EXAMPLE 8.

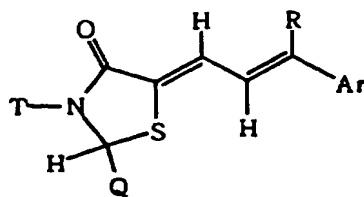
Preparation of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(3,5-dimethyl-4-ethoxycarbonyloxyphenylallylidene)-thiazolidine-4-one (Compound No. 175)

To a solution of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(3,5-dimethyl-4-hydroxyphenylallylidene)-thiazolidine-4-one(0.537 g, 1.31 mmol) in pyridine(5 mL) was added ethyl chloroformate(0.284 g, 2.62 mmol), stirred at room temperature for 3 h, and evaporated. The residue was neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate(4 x 20 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel to give 1.35 g (83 %) of 3-(2-*N,N*-dimethylaminoethyl)-2-(3-pyridyl)-5-(3,5-dimethyl-4-ethoxycarbonyloxyphenylallylidene)-thiazolidine-4-one.

¹H NMR(300 MHz, CDCl₃) δ : 8.65~8.61(m, 2H), 7.68(m, 1H), 7.35(m, 1H), 7.21(d, *J*=11.1Hz, 1H), 7.10(s, 2H), 6.72(d, *J*=15.3Hz, 1H), 6.55(dd, *J*=15.3, 11.1Hz, 1H), 3.99(m, 1H), 3.53(q, *J*=7.6Hz, 2H), 2.83(m, 1H), 2.65(m, 1H), 2.30(m, 1H), 2.24(s, 6H), 2.19(s, 6H), 1.25(t, *J*=7.6Hz, 3H)

The thiazolidin-4-one derivatives of formula(I) as shown in Table 3, Table 4, and Table 5 were prepared in the same manner as described in EXAMPLE 6 to EXAMPLE 8 using the intermediates of formula(II).

Table 3



5

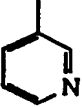
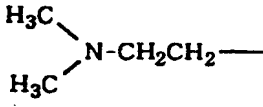
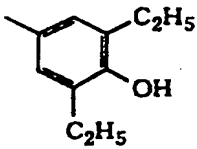
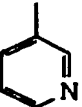
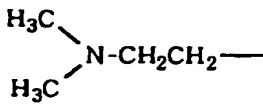
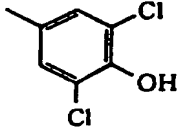
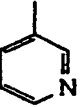
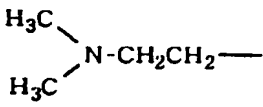
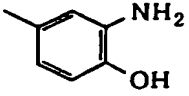
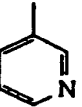
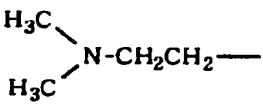
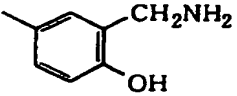
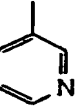
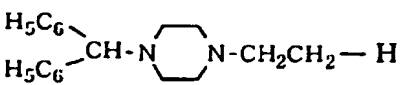
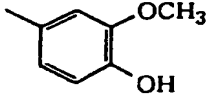
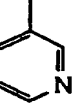
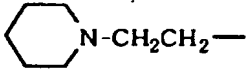
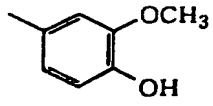
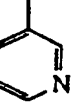
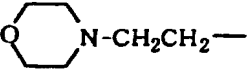
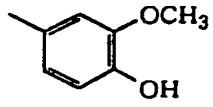
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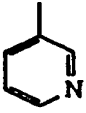
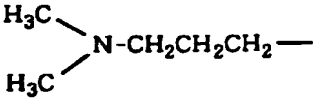
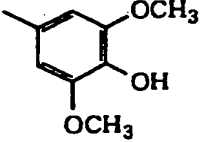
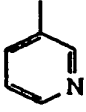
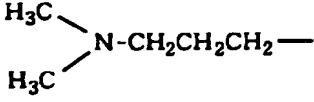
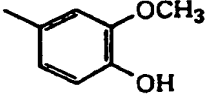
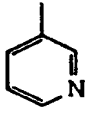
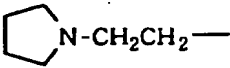
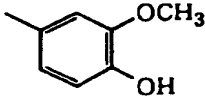
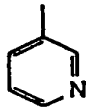
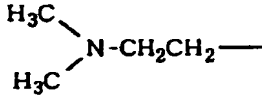
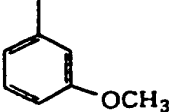
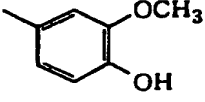

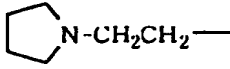
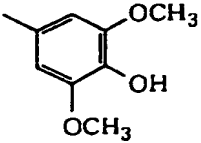
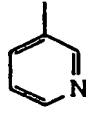
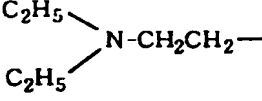
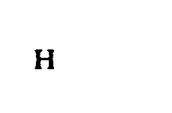
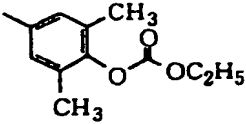
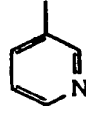
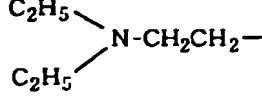
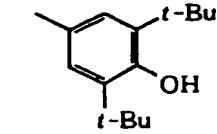
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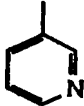
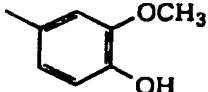
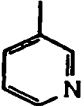
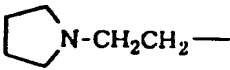
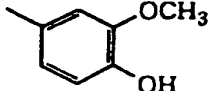
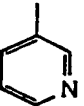
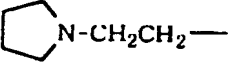
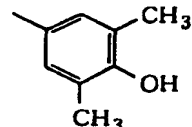
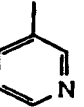
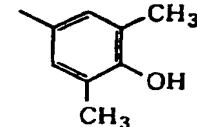
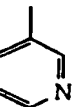
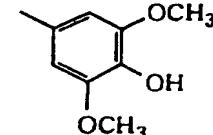
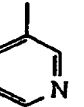
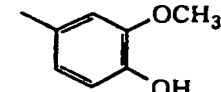
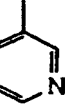
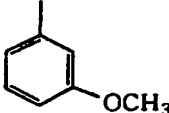
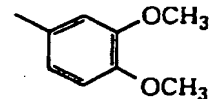
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25

Comp. No.	Q	T	R	Ar	Salt
148			H		
149			H		
150			H		
151			H		
152			H		
153			H		

Comp. No.	Q	T	R	Ar	Salt
5	154			H	
	155			H	
10	156			H	
	157			H	
15	158				
20	159			H	
	160			H	

Comp. No.	Q	T	R	Ar	Salt
5	161				
	162				
10	163				
	164				
15	165				
	166				
25	167				

Comp. No.	Q	T	R	Ar	Salt
5 168		$\begin{matrix} \text{H}_3\text{C} \\ \diagup \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagdown \\ \text{H}_3\text{C} \end{matrix}$	CH_3CH_2-		
169			H		
10 170			H		
15 171		$\begin{matrix} \text{C}_2\text{H}_5 \\ \diagup \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagdown \\ \text{C}_2\text{H}_5 \end{matrix}$	H		
172		$\begin{matrix} \text{C}_2\text{H}_5 \\ \diagup \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagdown \\ \text{C}_2\text{H}_5 \end{matrix}$	H		
20 173		$\begin{matrix} \text{C}_2\text{H}_5 \\ \diagup \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagdown \\ \text{C}_2\text{H}_5 \end{matrix}$	H		
25 174		$\begin{matrix} \text{H}_3\text{C} \\ \diagup \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagdown \\ \text{H}_3\text{C} \end{matrix}$			

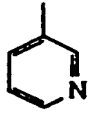
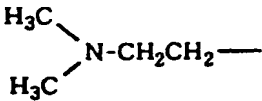
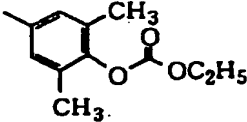
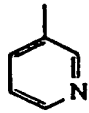
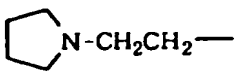
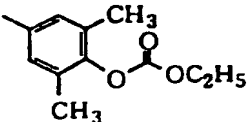
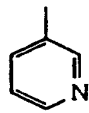
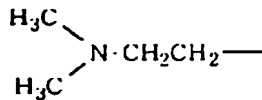
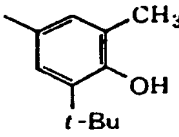
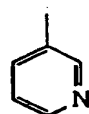
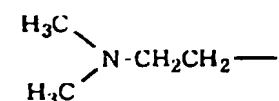
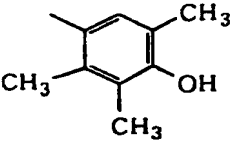
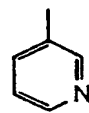
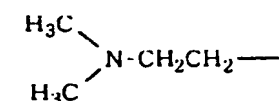
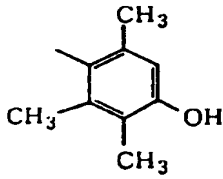
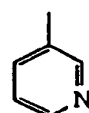
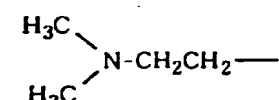
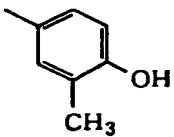
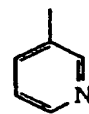
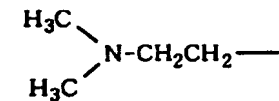
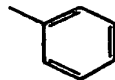
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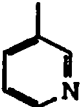
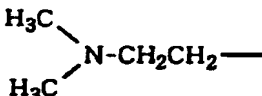
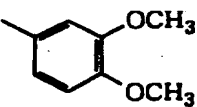

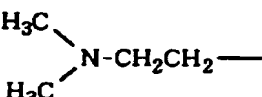
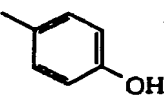
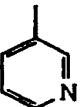
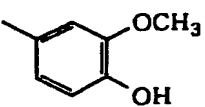
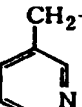
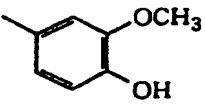
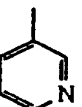
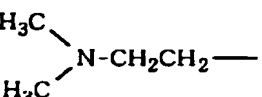
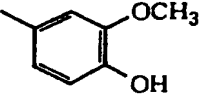
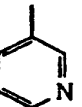
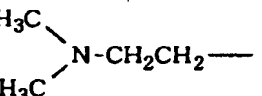
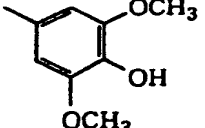
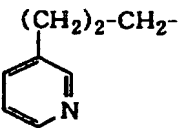
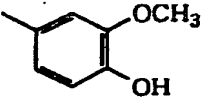
10

15

20

25

Comp. No.	Q	T	R	Ar	Salt
175			H		
176			H		
177			H		
178			H		
179			H		
180			H		
181			H		

Comp. No.	Q	T	R	Ar	Salt
5	182			H	
	183			H	
10	184		CH ₃ -	H	
	185		CH ₃ -	H	
15	186			CH ₃ CH ₂ CH ₂ -	
20	187			CH ₃ CH ₂ -	
25	188		CH ₃ -	H	

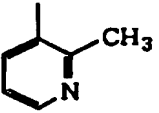
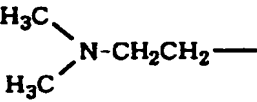
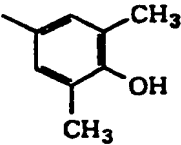
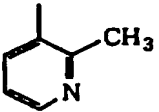
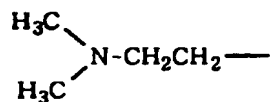
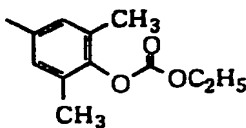
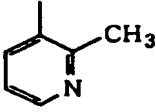
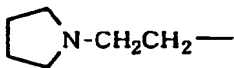
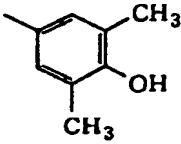
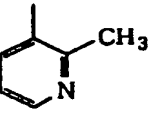
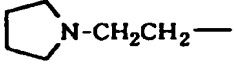
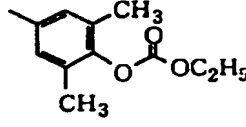
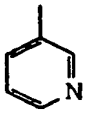
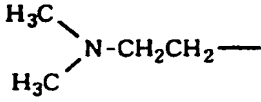
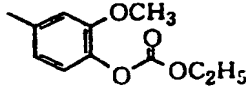
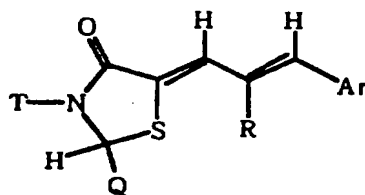
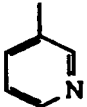
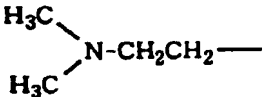
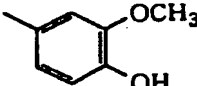
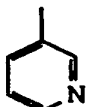
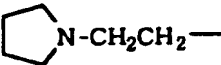
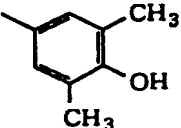
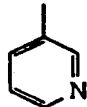
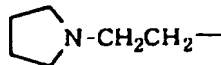
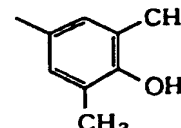
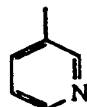
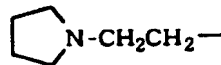
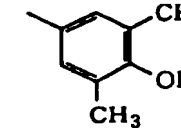
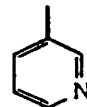
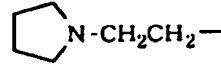
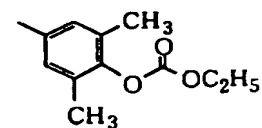
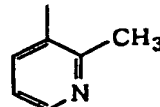
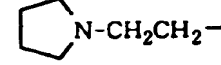
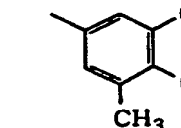
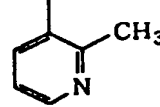

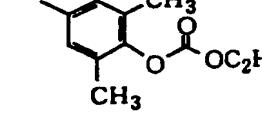
Comp. No.	Q	T	R	Ar	Salt
189			H		
190			H		
191			H		
192			H		
193			H		

Table 4



Comp. No.	Q	T	R	Ar	Salt
194		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{—}$	$\text{CH}_3\text{—}$		
195		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{—}$	$\text{CH}_3\text{CH}_2\text{—}$		
196		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{—}$	$\text{CH}_3\text{CH}_2\text{CH}_2\text{—}$		
197		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{—}$	$\text{CH}_3\text{—}$		
198		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{—}$	$\text{CH}_3\text{—}$		
199		$\begin{matrix} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{matrix} \text{N-CH}_2\text{CH}_2\text{—}$	$\text{CH}_3\text{CH}_2\text{—}$		

Comp. No.	Q	T	R	Ar	Salt
200			CH ₃ CH ₂ CH ₂ -		
201			CH ₃ -		
202			CH ₃ CH ₂ -		
203			CH ₃ CH ₂ CH ₂ -		
204			CH ₃ -		
205			CH ₃ -		
206			CH ₃ -		

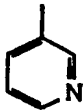
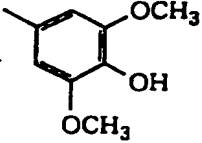
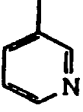
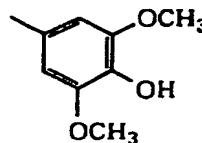
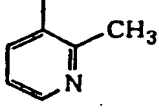
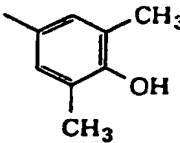
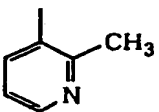
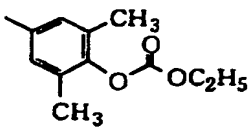
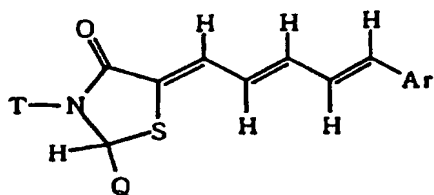
Comp. No.	Q	T	R	Ar	Salt
207		$\begin{matrix} \text{H}_3\text{C} \\ \diagdown \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagup \\ \text{H}_3\text{C} \end{matrix}$	$\text{CH}_3\text{CH}_2\text{CH}_2-$		
208		$\begin{matrix} \text{H}_3\text{C} \\ \diagdown \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagup \\ \text{H}_3\text{C} \end{matrix}$	CH_3CH_2-		
209		$\begin{matrix} \text{H}_3\text{C} \\ \diagdown \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagup \\ \text{H}_3\text{C} \end{matrix}$	CH_3-		
210		$\begin{matrix} \text{H}_3\text{C} \\ \diagdown \\ \text{N}-\text{CH}_2\text{CH}_2- \\ \diagup \\ \text{H}_3\text{C} \end{matrix}$	CH_3-		

Table 5



Comp. No.	Q	T	Ar
211			
212			

Also NMR datas of the compounds of formula(I) according to the present invention were listed as shown in Table 6.

NMR solvent ; CDCl_3

DMSO-d_6 (Hydrochloride salts of formula(I))

Table 6

Comp. No.		¹ H NMR(300 MHz) δ
5	1	9.70(s, 1H), 8.79(s, 1H), 8.69(d, $J=4.5$ Hz, 1H), 7.97(d, $J=8.1$ Hz, 1H), 7.60~7.55(m, 6H), 6.39(s, 1H), 4.20~4.12(m, 1H), 3.21~3.00(m, 3H), 2.82(d, $J=3.9$ Hz, 6H)
	2	8.65(m, 2H), 7.70(m, 1H), 7.50(s, 1H), 7.38(m, 1H), 7.18(d, $J=8.4$ Hz, 1H), 7.05(s, 1H), 6.85(d, $J=8.4$ Hz, 1H), 6.18(s, 1H), 4.05(m, 1H), 3.90
10		(s, 3H), 3.89(s, 3H), 2.82(m, 1H), 2.59(m, 1H), 2.38(m, 1H), 2.18(s, 6H)
	3	8.63(m, 2H), 7.66(m, 1H), 7.50(s, 1H), 7.36(m, 1H), 6.74(s, 2H), 6.18(s, 1H), 3.98(m, 1H), 3.87(s, 3H), 3.86(s, 3H), 3.85(s, 3H), 2.82(m, 1H), 2.69(m, 1H), 2.38(m, 1H), 2.18(s, 6H)
15	4	9.70(brs, 1H), 8.74(s, 1H), 8.64(m, 1H), 7.84(m, 1H), 7.80(m, 1H), 7.66
		(s, 1H), 7.58(m, 2H), 7.49(m, 1H), 6.38(s, 1H), 4.15(m, 1H), 3.38(m, 1H), 3.00~3.20(m, 2H), 2.82(s, 6H)
20	6	10.14(brs, 1H), 9.95(s, 1H), 8.79(d, $J=4.5$ Hz, 1H), 8.22(d, $J=8.1$ Hz, 1H), 7.78(dd, $J=8.1, 4.5$ Hz, 1H), 7.31(s, 1H), 6.97(s, 1H), 6.85(s, 2H), 6.46(s, 1H), 4.15(m, 1H), 3.65(m, 1H), 3.40(m, 1H), 3.15(m, 1H), 2.87
		(d, $J=3.6$ Hz, 6H)
25	7	8.62(m, 2H), 7.68(m, 1H), 7.50(s, 1H), 7.37(d, $J=9.0$ Hz, 2H), 7.35(m, 1H), 6.67(d, $J=9.0$ Hz, 2H), 6.11(s, 1H), 3.97(m, 1H), 3.38(q, $J=7.2$ Hz, 4H), 2.85(m, 1H), 2.55(m, 1H), 2.14(m, 1H), 2.18(s, 6H), 1.17(t, $J=7.2$ Hz, 6H)
	8	8.60(m, 2H), 7.95(s, 1H), 7.70(m, 2H), 7.54(m, 2H), 7.42(m, 1H), 7.38
		(m, 1H), 6.17(s, 1H), 4.10(m, 1H), 2.85(m, 1H), 2.60(m, 1H), 2.37(m, 1H), 2.18(s, 6H)

Comp. No.		¹ H NMR(300 MHz) δ
5	9	10.02(m, 2H), 8.88(brs, 1H), 8.77(brs, 1H), 8.13(m, 1H), 7.74(s, 2H), 7.15(d, $J=8.7$ Hz, 1H), 6.45(s, 1H), 6.39(m, 1H), 6.32(m, 1H), 4.62(brs, 1H), 4.12(m, 1H), 3.40(m, 1H), 3.15(m, 2H), 2.80(s, 6H)
	10	9.87(brs, 1H), 8.86(d, $J=1$ Hz, 1H), 8.75(d, $J=4.5$ Hz, 1H), 8.17(d, $J=7.6$ Hz 1H), 7.75(dd, $J=7.6, 4.5$ Hz, 1H), 7.34(s, 1H), 7.12(s, 2H), 6.39(s, 1H), 4.05(m, 1H), 3.15(m, 3H), 2.81(s, 6H), 2.17(s, 6H)
10	11	8.61(m, 2H), 7.75(m, 1H), 7.54(s, 1H), 7.41(s, 2H), 7.38(m, 1H), 6.15(s, 1H), 4.20(m, 1H), 2.85(m, 1H), 2.62(m, 1H), 2.38(m, 1H), 2.19(s, 6H), 1.43(s, 18H)
	12	8.62(m, 2H), 7.68(m, 1H), 7.54(s, 1H), 7.45(d, $J=9.0$ Hz, 2H), 7.27(m, 1H), 6.94(d, $J=9.0$ Hz, 2H), 6.15(s, 1H), 3.98(m, 1H), 3.83(s, 3H), 2.85(m, 1H)
15	13	8.65(m, 1H), 8.61(m, 1H), 7.86(s, 1H), 7.66(m, 1H), 7.43–7.55(m, 2H), 7.30(m, 1H), 7.26(m, 1H), 6.19(s, 1H), 4.01(m, 1H), 2.87(m, 1H), 2.59(m, 1H), 2.36(m, 1H), 2.19(s, 6H)
	14	9.79(brs, 1H), 8.82(s, 1H), 8.72(m, 1H), 8.03(m, 1H), 7.83(s, 1H), 7.65(m, 1H), 6.83(m, 2H), 6.72(m, 1H), 6.35(s, 1H), 4.14(m, 1H), 3.42(m, 1H), 3.10(m, 2H), 2.82(m, 6H)
20	15	9.72(brs, 1H), 9.43(brs, 1H), 8.80(brs, 1H), 8.70(brs, 1H), 7.98(m, 1H), 7.75(s, 1H), 7.62(m, 1H), 6.82(m, 1H), 6.75(m, 1H), 6.62(m, 1H), 6.35(s, 1H), 4.15(m, 1H), 3.40(m, 1H), 3.10(m, 2H), 2.82(m, 6H)
	16	9.50(brs, 1H), 9.00(brs, 1H), 8.72(m, 1H), 8.66(m, 1H), 7.88(m, 1H), 7.78(s, 1H), 7.50(m, 1H), 6.72(d, $J=8.7$ Hz, 1H), 6.40(d, $J=8.7$ Hz, 1H), 6.25(s, 1H), 4.12(m, 1H), 3.36(m, 1H), 3.08(m, 2H), 2.80(m, 6H)

Comp. No.	¹ H NMR(300 MHz) δ
17	8.65(m, 1H), 8.60(m, 1H), 7.66(m, 1H), 7.39~7.49(m, 5H), 7.20~7.39
5	(m, 7H), 7.09(d, J=1.8Hz, 1H), 7.03(m, 1H), 6.94(m, 1H), 6.12(s, 1H), 5.19(s, 2H), 5.17(s, 2H), 3.98(m, 1H), 2.84(m, 1H), 2.54(m, 1H), 2.33(m, 1H), 2.18(s, 6H)
22	10.09(brs, 1H), 8.99(s, 1H), 8.82(d, J=4.8Hz, 1H), 8.29(d, J=8.1Hz, 1H), 7.83(dd, J=7.8, 5.4Hz, 1H), 7.45(s, 1H), 7.38(t, J=7.8Hz, 1H), 7.10
10	(d, J=7.8Hz, 1H), 7.06(s, 1H), 6.94(dd, J=8.4, 1.8Hz, 1H), 6.52(s, 1H), 4.15(m, 1H), 3.82(s, 3H), 3.04~3.27(m, 2H), 2.81(s, 6H)
23	9.77(brs, 1H), 8.82(m, 1H), 8.74(m, 1H), 8.02(m, 1H), 7.64(m, 1H), 7.43
15	(s, 1H), 6.82(s, 2H), 6.38(s, 1H), 4.15(m, 1H), 3.93(t, J=6.3Hz, 4H), 3.86(t, J=6.3Hz, 2H), 2.96~3.37(m, 3H), 2.81(s, 6H), 1.73(m, 4H), 1.65 (m, 2H), 0.98(m, 9H)
38	8.59(m, 2H), 7.62(m, 1H), 7.47(s, 1H), 7.32(m, 1H), 7.16(s, 2H), 6.21(s, 1H), 3.82(m, 1H), 2.85(m, 2H), 2.45(m, 5H), 2.29(s, 6H), 0.95(t, J=
39	6.9Hz, 6H)
20	10.1(brs, 1H), 8.93(s, 1H), 8.81(m, 1H), 8.24(m, 1H), 7.79(m, 1H), 7.31 (s, 1H), 6.96(s, 1H), 6.83(m, 2H), 6.24(s, 1H), 4.04(m, 1H), 3.24(m, 2H), 3.13(m, 4H), 1.17(t, J=7.2Hz, 6H)
40	8.62(m, 2H), 7.68(m, 2H), 7.53(s, 1H), 7.35(m, 1H), 7.08(d, J=8.2Hz, 1H), 7.05(s, 1H), 6.90(d, J=8.2Hz, 1H), 6.19(s, 1H), 4.01(m, 1H), 3.90 (s, 3H), 3.89(s, 3H), 2.80~3.02(m, 2H), 2.48(m, 5H), 1.77(m, 4H)

Comp. No.	¹ H NMR(300 MHz) δ
5	47 8.63(m, 2H), 7.67(m, 1H), 7.53(s, 1H), 7.35(m, 1H), 7.08(d, $J=8.4$ Hz, 1H), 7.05(s, 1H), 6.90(d, $J=8.4$ Hz, 1H), 6.21(s, 1H), 3.95(m, 1H), 3.90(s, 6H), 2.91(m, 1H), 2.82(m, 1H), 2.35(m, 5H), 1.57(m, 1H), 1.44(m, 2H)
10	50 8.65(m, 1H), 8.61(m, 1H), 7.71(m, 1H), 7.53(s, 1H), 7.36(m, 1H), 7.09(d, $J=8.4$ Hz, 1H), 7.05(s, 1H), 6.91(d, $J=8.4$ Hz, 1H), 6.14(s, 1H), 3.96(m, 1H), 3.90(s, 3H), 3.89(s, 3H), 3.69(m, 4H), 2.93(m, 1H), 2.61(m, 1H), 2.43(m, 1H), 2.41(m, 4H)
15	67 8.81(s, 1H), 8.76(d, $J=4.8$ Hz, 1H), 8.08(d, $J=8.1$ Hz, 1H), 7.73(m, 1H), 7.16~7.29(m, 6H), 6.95(s, 1H), 6.83(s, 2H), 6.22(s, 1H), 3.92(m, 1H), 3.05(m, 1H), 2.95(m, 1H), 2.89(m, 1H)
15	69 8.60(s, 1H), 8.59(s, 1H), 7.72(d, $J=7.8$ Hz, 1H), 7.45(m, 1H), 7.40(s, 1H), 6.99~7.27(m, 8H), 6.03(s, 1H), 3.95(m, 1H), 3.80(s, 3H), 3.79(s, 3H), 2.80~3.05(m, 2H), 2.60~2.80(m, 1H)
20	71 8.79(s, 1H), 8.75(d, $J=4.8$ Hz, 1H), 8.08(d, $J=8.1$ Hz, 1H), 7.72(m, 1H), 7.39(s, 1H), 7.27(s, 2H), 7.17(m, 5H), 6.20(s, 1H), 4.05(m, 1H), 3.05(m, 1H), 2.92(m, 1H), 2.85(m, 1H), 1.37(s, 18H)
25	72 8.62(d, $J=5.1$ Hz, 1H), 8.39(s, 1H), 7.61~7.51(m, 2H), 7.40~7.30(m, 1H), 7.07(dd, $J=8.1, 2.1$ Hz, 1H), 7.03(d, $J=2.1$ Hz, 1H), 6.91(d, $J=8.1$ Hz, 1H), 6.83(d, $J=8.1$ Hz, 1H), 6.68(dd, $J=8.1, 1.5$ Hz, 1H), 6.64(d, $J=1.5$ Hz, 1H), 5.26(s, H), 4.10(m, 1H), 3.90(s, 3H), 3.89(s, 3H), 3.88(s, 3H), 3.82(s, 3H), 3.05~2.70(m, 3H)

Comp. No.	¹ H NMR(300 MHz) δ
5	74 8.76(m, 2H), 8.05(m, 1H), 7.71(m, 1H), 7.40(s, 1H), 7.11(s, 1H), 7.05(s, 1H), 6.83(d, $J=8.4\text{Hz}$), 6.73(s, 1H), 6.65(d, $J=8.4\text{Hz}$), 6.15(s, 1H), 4.05(m, 1H), 3.78(s, 3H), 3.76(s, 3H), 3.05(m, 1H), 2.80(m, 1H), 2.65(m, 1H), 2.17(s, 6H)
10	78 8.65(d, $J=3.9\text{Hz}$, 1H), 8.50(s, 1H), 7.70(d, $J=8.1\text{Hz}$, 1H), 7.61(s, 1H), 7.40(m, 1H), 7.10(d, $J=6.9\text{Hz}$, 1H), 7.04(s, 1H), 6.89(d, $J=8.1\text{Hz}$, 1H), 6.70(d, $J=7.8\text{Hz}$, 1H), 6.67(s, 1H), 6.52(d, $J=7.8\text{Hz}$), 5.96(s, 2H), 5.61(s, 1H), 4.44(ABq, $\Delta\nu=477$, $J_{AB}=14.4\text{Hz}$, 2H), 3.90(s, 3H), 3.89(s, 3H)
15	79 8.72(m, 2H), 8.06(d, $J=6.2\text{Hz}$, 1H), 7.71(m, 1H), 7.36(s, 1H), 6.95(s, 1H), 6.79(m, 3H), 6.69(s, 1H), 6.58(d, $J=7.8\text{Hz}$, 1H), 6.13(s, 1H), 5.97(s, 2H), 4.43(ABq, $\Delta\nu=228$, $J_{AB}=15.3\text{Hz}$, 2H)
20	80 8.78~8.76(m, 2H), 8.15(d, $J=8.1\text{Hz}$), 7.77(dd, $J=8.1, 5.4\text{Hz}$, 1H), 7.51(s, 1H), 7.30(s, 2H), 6.78(d, $J=8.1\text{Hz}$, 1H), 6.70(s, 1H), 6.58(d, $J=8.1\text{Hz}$, 1H), 6.17(s, 1H), 5.99(s, 2H), 4.45(ABq, $\Delta\nu=205.5$, $J_{AB}=15\text{Hz}$, 2H), 1.38(s, 18H)
25	81 8.60(m, 2H), 8.52(m, 1H), 7.71(m, 1H), 7.66(m, 1H), 7.60(s, 1H), 7.46(d, $J=8.7\text{Hz}$, 2H), 7.35(m, 1H), 7.22(m, 1H), 6.94(d, $J=8.7\text{Hz}$, 2H), 6.04(s, 1H), 5.21(d, $J=15.3\text{Hz}$, 1H), 4.04(d, $J=15.3\text{Hz}$, 1H), 3.83(s, 3H)
	82 8.56~8.67(m, 2H), 8.52(m, 1H), 7.72(m, 1H), 7.65(m, 1H), 7.59(s, 1H), 7.34(m, 1H), 7.27(d, $J=6.6\text{Hz}$, 1H), 7.20(m, 1H), 7.10(m, 1H), 7.06(m, 1H), 6.91(d, $J=6.6\text{Hz}$, 1H), 6.04(s, 1H), 5.22(d, $J=15.3\text{Hz}$, 1H), 4.03(d, $J=15.3\text{Hz}$, 1H), 3.91(s, 3H), 3.90(s, 3H)

Comp. No.	¹ H NMR(300 MHz) δ
5	83 8.62(m, 2H), 8.53(m, 2H), 7.73(m, 1H), 7.66(m, 1H), 7.56(s, 1H), 7.35(m, 1H), 7.21(m, 1H), 6.76(s, 2H), 6.07(s, 1H), 5.22(d, $J=15.3\text{Hz}$, 1H), 4.04(d, $J=15.3\text{Hz}$, 1H), 3.87(s, 9H)
	84 8.82(s, 1H), 8.73(m, 1H), 8.55(m, 1H), 8.20(m, 1H), 7.95(m, 1H), 7.74(m, 1H), 7.43(m, 2H), 7.35(s, 1H), 6.98(m, 1H), 6.85(m, 2H), 6.36(s, 1H), 5.01(d, $J=16.2\text{Hz}$, 1H), 4.36(d, $J=16.2\text{Hz}$, 1H)
10	85 8.70(m, 2H), 7.90(m, 1H), 7.58(m, 1H), 7.43(s, 1H), 6.85(s, 2H), 6.30(s, 1H), 3.42(m, 1H), 1.42(m, 2H), 0.98(t, $J=7.6\text{Hz}$, 3H)
15	86 8.62(m, 1H), 8.53(m, 1H), 8.49(m, 1H), 7.61(m, 2H), 7.50(s, 1H), 7.33(m, 1H), 7.19(m, 2H), 7.07(m, 1H), 7.02(m, 1H), 6.90(m, 1H), 5.65(s, 1H), 4.20(m, 1H), 3.90(s, 3H), 3.89(s, 3H), 3.31(m, 1H), 3.14(m, 1H), 3.06(m, 1H)
	87 8.61(m, 1H), 8.44~8.57(m, 2H), 7.60~7.74(m, 2H), 7.51(s, 1H), 7.18~7.37(m, 4H), 7.07(d, $J=7.5\text{Hz}$, 1H), 7.01(s, 1H), 6.90(m, 1H), 5.73(s, 1H), 4.21(m, 1H), 3.81(s, 3H), 3.30(m, 1H), 3.17(m, 2H)
20	88 8.62(m, 1H), 8.53(m, 1H), 8.48(m, 1H), 7.56~7.70(m, 2H), 7.51(s, 1H), 7.43(d, $J=8.7\text{Hz}$, 2H), 7.29~7.37(m, 1H), 7.12~7.23(m, 2H), 6.93(d, $J=8.7\text{Hz}$, 2H), 5.63(s, 1H), 4.21(m, 1H), 3.82(s, 3H), 3.30(m, 1H), 3.15(m, 1H), 3.05(m, 1H)
	89 8.72(m, 2H), 8.25(m, 1H), 7.93(m, 1H), 7.74(m, 2H), 7.60(m, 1H), 7.21(s, 1H), 7.07(s, 2H), 6.33(s, 1H), 4.12(m, 1H), 3.20(m, 3H), 2.16(s, 6H)

Comp. No.	¹ H NMR(300 MHz) δ
5	90 8.69(m, 2H), 8.37(s, 1H), 7.78(d, $J=7.8$ Hz, 1H), 7.50(s, 1H), 7.41(m, 1H), 6.74(s, 2H), 5.99(s, 1H), 4.40(m, 1H), 4.13(m, 1H), 3.87(s, 9H), 3.17(d, $J=14.4$ Hz, 1H), 3.05(d, $J=14.4$ Hz, 1H), 2.04(s, 3H)
10	91 9.90(brs, 1H), 8.89(s, 1H), 8.78(m, 1H), 8.20(d, $J=7.6$ Hz, 1H), 7.79(m, 1H), 7.42(s, 1H), 7.08(m, 3H), 6.35(s, 1H), 3.89(m, 1H), 3.85(m, 1H), 3.78(s, 3H), 3.77(s, 3H), 3.61(m, 1H), 3.00(m, 1H), 1.94(s, 3H)
15	92 8.68(s, 2H), 8.42(s, 1H), 7.78(d, $J=7.6$ Hz, 1H), 7.52(s, 1H), 7.41(m, 1H), 7.10(d, $J=8.4$ Hz, 1H), 7.03(s, 1H), 6.90(d, $J=8.4$ Hz, 1H), 6.00(s, 1H), 5.20(brs, 2H), 4.08(m, 2H), 3.91(s, 3H), 3.89(s, 3H), 3.14(m, 2H)
20	93 10.54(s, 1H), 8.83(s, 1H), 8.64(m, 1H), 7.77(d, $J=7.8$ Hz, 1H), 7.48(m, 1H), 7.44(s, 1H), 6.88(s, 2H), 6.24(s, 1H), 3.86(m, 1H), 3.79(s, 6H), 3.69(s, 3H), 3.02(m, 1H), 2.38(m, 1H), 2.15(m, 1H)
25	94 8.64(s, 1H), 8.49(d, $J=2.4$ Hz, 1H), 7.74(d, $J=7.5$ Hz, 1H), 7.42(s, 1H), 6.96(d, $J=8.4$ Hz, 1H), 6.93(s, 1H), 6.78(d, $J=8.4$ Hz, 1H), 6.12(s, 1H), 4.38(d, $J=15.9$ Hz, 1H), 3.89(s, 3H), 3.84(s, 3H), 3.54(d, $J=15.9$ Hz, 1H)
	95 8.71(s, 1H), 8.50(m, 1H), 8.32(d, $J=8.4$ Hz, 1H), 8.24(s, 1H), 7.72(m, 3H), 7.26(m, 1H), 7.09(m, 4H), 6.92(d, $J=8.4$ Hz, 1H), 3.92(s, 6H)
	96 8.70(m, 1H), 8.47(m, 1H), 8.26(m, 2H), 7.69(m, 3H), 7.20(m, 1H), 7.07(s, 1H), 7.05(m, 1H), 6.79(s, 2H), 3.83(s, 3H), 3.82(s, 3H), 3.78(s, 3H)
	97 8.72(m, 1H), 8.43(m, 1H), 8.24(m, 1H), 8.09(m), 7.67(m, 2H), 7.39(d, $J=8.4$ Hz, 2H), 7.20(m, 1H), 7.07(s, 1H), 7.05(m, 1H), 6.71(d, $J=8.4$ Hz, 2H), 6.49(s, 1H), 3.84(s, 3H)

Comp. No.		¹ H NMR(300 MHz) δ
5	98	8.53(m, 1H), 8.46(s, 1H), 7.52(m, 3H), 7.17(m, 1H), 7.07(d, $J=8.1$ Hz, 1H), 7.02(s, 1H), 6.91(d, $J=8.1$ Hz, 1H), 5.62(s, 1H), 4.79(m, 1H), 4.40(m, 1H), 4.15(m, 1H), 3.92(s, 3H), 3.90(s, 3H), 3.61(s, 3H),
	99	8.62(m, 2H), 8.05(s, 1H), 7.82(d, $J=7.8$ Hz, 1H), 7.49(s, 1H), 7.38(m, 1H), 7.03(s, 2H), 6.00(s, 1H), 3.90(s, 3H), 3.89(s, 3H), 3.88(s, 3H)
	100	9.56(s, 1H), 8.81(s, 1H), 8.71(m, 1H), 8.20(d, $J=8.1$ Hz, 1H), 7.74(m, 1H), 7.22(s, 1H), 7.08(s, 2H), 6.26(s, 1H), 2.17(s, 6H)
10	101	8.65(m, 2H), 8.06(s, 1H), 7.82(m, 1H), 7.50(s, 1H), 7.39(m, 1H), 7.09(d, $J=8.3$ Hz, 2H), 6.89(d, $J=8.3$ Hz, 2H), 6.01(s, 1H), 3.91(s, 3H)
	102	9.97(s, 1H), 8.83(s, 1H), 8.73(d, $J=5.1$ Hz, 1H), 8.20(d, $J=7.8$ Hz), 7.76(s, 1H), 7.74(m, 1H), 7.56(s, 3H), 6.36(s, 1H)
	103	9.56(s, 1H), 8.81(d, $J=1.5$ Hz, 1H), 8.72(d, $J=4.8$ Hz), 8.19(d, $J=8.1$ Hz, 1H), 7.75(m, 1H), 7.20(s, 1H), 6.93(s, 1H), 6.81(s, 2H), 6.26(s, 1H)
15	107	DMSO-d ₆ ; 9.56(s, 1H), 8.80(d, $J=1.5$ Hz, 1H), 8.71(d, $J=4.2$ Hz, 1H), 8.15(d, $J=8.1$ Hz, 1H), 7.73(dd, $J=7.8, 5.1$ Hz, 1H), 7.33(s, 1H), 7.27(s, 2H), 6.25(s, 1H), 4.8(brs, 1H), 1.38(s, 18H)
	109	8.65(m, 1H), 8.61(m, 1H), 7.68(m, 1H), 7.53(s, 1H), 7.36(m, 1H), 7.04(m, 2H), 6.90(m, 1H), 5.82(s, 1H), 4.13(q, $J=6.9$ Hz, 2H), 3.89(s, 3H), 3.88(m, 1H), 2.79(m, 1H), 1.52(m, 2H), 1.47(t, $J=6.9$ Hz, 3H), 1.28(m, 2H), 0.89(t, $J=7.5$ Hz, 3H)
	110	8.80(s, 1H), 8.72(m, 1H), 8.06(m, 1H), 7.66(m, 1H), 7.42(s, 1H), 7.01~7.17(m, 3H), 6.33(s, 1H), 3.78(s, 3H), 3.77(s, 3H), 3.68(m, 1H), 2.79(m, 1H), 1.42(m, 2H), 1.20(m, 2H), 0.83(t, $J=4.5$ Hz, 3H)
25		

Comp. No.	¹ H NMR(300 MHz) δ
111	8.83(s, 1H), 8.74(s, 1H), 8.10(brs, 1H), 7.74(brs, 1H), 7.28(s, 1H), 6.95
5	(s, 1H), 6.81(m, 2H), 6.32(s, 1H), 4.25(brs, 2H), 3.75(m, 1H), 2.78(m, 1H), 1.43(m, 2H), 1.22(m, 2H), 0.85(t, $J=6.3$ Hz, 3H)
112	8.63(m, 2H), 7.67(m, 1H), 7.53(s, 1H), 7.38(m, 1H), 7.05(d, $J=8.4$ Hz, 1H), 7.04(s, 1H), 6.89(d, $J=8.4$ Hz, 1H), 5.82(s, 1H), 4.00(t, $J=6.9$ Hz, 2H), 3.92(m, 1H), 3.88(s, 3H), 2.80(m, 1H), 1.88(m, 2H), 1.52(m, 2H),
10	1.32(m, 2H), 1.01(t, $J=7.2$ Hz, 3H), 0.89(t, $J=7.5$ Hz, 3H)
115	8.66(d, $J=3.6$ Hz, 1H), 8.62(d, $J=1.5$ Hz, 1H), 7.68(d, $J=8.1$ Hz, 1H), 7.54(s, 1H), 7.37(dd, $J=8.1, 3.6$ Hz, 1H), 7.10(dd, $J=8.4, 1.8$ Hz, 1H), 7.05(s, 1H), 6.91(d, $J=8.4$ Hz, 1H), 5.72(s, 1H), 3.90(s, 6H), 2.91(s, 3H)
116	9.39(s, 1H), 9.18(s, 1H), 8.61~8.60(m, 2H), 7.74(d, $J=8.1$ Hz, 1H), 7.47
15	(dd, $J=8.1, 4.8$ Hz, 1H), 7.27(s, 1H), 6.97(d, $J=1.5$ Hz), 6.85(dd, $J=8.4, 1.5$ Hz, 1H), 6.80(d, $J=8.4$ Hz, 1H), 6.12(s, 1H), 3.34(s, 2H), 2.80(s, 3H)
117	8.92(d, $J=1.2$ Hz, 1H), 8.44(d, $J=4.8$ Hz, 1H), 8.28(d, $J=8.1$ Hz, 1H), 7.89(dd, $J=8.1, 4.8$ Hz, 1H), 7.49(s, 1H), 7.11(d, $J=1.8$ Hz, 1H), 6.98(dd, $J=8.4, 1.8$ Hz, 1H), 6.88(d, $J=8.4$ Hz, 1H), 6.28(s, 1H), 5.40(brs, 3H),
20	3.78(s, 3H), 2.84(s, 3H)
118	7.26(s, 1H), 6.99(s, 1H), 6.87(d, $J=8.4$ Hz, 1H), 6.78(d, $J=8.4$ Hz, 1H), 4.96(d, $J=6.3$ Hz, 1H), 4.1(brs, 2H, 2OH), 3.25(m, 1H), 2.66(m, 2H), 2.39(s, 6H), 1.87~2.05(m, 1H), 1.56~1.79(m, 1H), 1.31~1.50(m, 12H), 0.87(t, $J=6.6$ Hz, 3H)

Comp. No.	¹ H NMR(300 MHz) δ
5	119 7.42(s, 1H), 7.14(d, $J=8.4$ Hz, 1H), 7.09(s, 1H), 6.92(d, $J=8.4$ Hz, 1H), 5.05(dd, $J=8.1, 2.1$ Hz, 1H), 3.98(m, 1H), 3.93(s, 3H), 3.91(s, 3H), 3.30 (m, 1H), 2.50(m, 1H), 2.29(s, 6H), 1.92(m, 1H), 1.74(m, 1H), 1.14~1.53 (m, 12H), 0.88(t, $J=6.3$ Hz, 3H)
10	120 7.36(s, 1H), 7.12(d, $J=1.8$ Hz, 1H), 6.98(d, $J=1.8$ Hz, 1H), 6.91(d, $J=$ 8.1Hz, 1H), 4.77(dd, $J=8.4, 1.8$ Hz, 1H), 3.06(s, 3H), 1.95~2.13(m, 1H), 1.65~1.82(m, 1H), 1.13~1.48(m, 12H), 0.88(t, $J=6.6$ Hz, 3H)
15	121 7.43(s, 1H), 7.14(dd, $J=8.4, 1.5$ Hz, 1H), 7.09(d, $J=1.5$ Hz, 1H), 6.92(d, $J=8.4$ Hz, 1H), 4.80(dd, $J=8.1, 1.8$ Hz, 1H), 3.93(s, 3H), 3.91(s, 3H), 3.07 (s, 3H), 1.97~2.13(m, 1H), 1.66~1.83(m, 1H), 1.15~1.52(m, 12H), 0.88 (t, $J=6.6$ Hz, 3H)
20	122 7.36(s, 1H), 7.12(d, $J=1.8$ Hz, 1H), 7.98(dd, $J=8.4, 1.8$ Hz, 1H), 6.91(d, $J=8.4$ Hz), 4.77(dd, $J=8.4, 2.7$ Hz, 1H), 3.06(s, 3H), 1.91~2.12(m, 1H), 1.63~1.81(m, 1H), 1.09~1.52(m, 8H), 0.88(t, $J=6.6$ Hz, 3H) 123 7.43(s, 1H), 7.14(dd, $J=8.4, 1.8$ Hz, 1H), 7.09(d, $J=1.8$ Hz, 1H), 6.94(d, $J=8.4$ Hz, 1H), 4.80(m, 1H), 3.93(s, 3H), 3.91(s, 3H), 3.07(s, 3H), 2.05 (m, 1H), 1.72(m, 1H), 1.30(m, 8H), 0.89(t, $J=6.6$ Hz, 3H) 124 8.03(brs, 2H), 7.33(s, 1H), 7.09(d, $J=1.8$ Hz, 1H), 6.96(dd, $J=8.4, 1.8$ Hz, 1H), 6.89(d, $J=8.4$ Hz, 1H), 4.79(dd, $J=8.1, 2.7$ Hz, 1H), 3.06(s, 3H), 1.95~2.12(m, 1H), 1.65~1.82(m, 1H), 1.32~1.55(m, 2H), 0.98(t, $J=$ 7.2Hz, 3H)

Comp. No.	¹ H NMR(300 MHz) δ
5	125 7.43(s, 1H), 7.14(dd, $J=8.4, 1.8\text{Hz}$, 1H), 7.09(d, $J=1.8\text{Hz}$, 1H), 6.92(d, $J=8.4\text{Hz}$, 1H), 4.80(dd, $J=8.1, 2.7\text{Hz}$, 1H), 3.93(s, 3H), 3.91(s, 3H), 3.07(s, 3H), 1.83~2.11(m, 1H), 1.64~1.84(m, 1H), 1.34~1.55(m, 2H), 0.99(t, $J=7.2\text{Hz}$, 3H)
10	126 8.59(s, 1H), 8.02(brs, 1H), 7.31~7.52(m, 10H), 6.19(s, 1H), 4.63(ABq, $\Delta\nu = 224$, $J_{AB}=16.2\text{Hz}$, 2H), 1.38(s, 18H) 130 7.51(s, 1H), 7.12(d, $J=8.4\text{Hz}$, 1H), 7.06(s, 1H), 6.91(d, $J=8.4\text{Hz}$, 1H), 6.55(s, 2H), 6.01(s, 1H), 4.01(m, 1H), 3.90(s, 6H), 3.85(s, 9H), 3.00(m, 1H), 2.58(m, 1H), 2.47(m, 1H), 2.26(s, 6H)
15	131 9.42(s, 1H), 9.21(s, 1H), 7.27(s, 1H), 6.97(s, 1H), 6.84(m, 2H), 6.76(s, 2H), 6.12(s, 1H), 4.12(m, 1H), 3.78(s, 6H), 3.67(s, 3H), 3.26(m, 3H), 2.81(s, 6H) 132 12.37(brs, 1H), 7.43(s, 1H), 7.16(s, 2H), 6.70(s, 2H), 6.10(s, 1H), 4.00(m, 1H), 3.87(s, 6H), 3.85(s, 3H), 3.68(m, 1H), 3.08~3.13(m, 2H), 2.87(d, $J=4.2\text{Hz}$, 3H), 2.79(d, $J=3.9\text{Hz}$, 3H), 2.26(s, 6H)
20	133 10.0(s, 1H), 9.76(s, 1H), 9.41(brs, 1H), 7.71(s, 1H), 7.18(d, $J=8.7\text{Hz}$, 1H), 6.75(s, 2H), 6.40(s, 1H), 6.30(d, $J=8.7\text{Hz}$, 1H), 6.07(s, 1H), 4.05(m, 1H), 3.78(s, 6H), 2.25(s, 6H)
25	138 8.63(m, 2H), 7.69(d, $J=7.8\text{Hz}$, 1H), 7.54(s, 1H), 7.35(m, 1H), 7.03~7.16(m, 2H), 6.91(d, $J=8.4\text{Hz}$, 1H), 6.12(s, 1H), 4.03(m, 1H), 3.91(s, 3H), 3.90(s, 3H), 3.62(m, 1H), 3.52(m, 1H), 3.32(s, 3H), 2.94(m, 1H)

Comp. No.		¹ H NMR(300 MHz) δ
5	139	8.62(m, 2H), 7.69(d, $J=8.1$ Hz, 1H), 7.54(s, 1H), 7.35(m, 1H), 7.03~7.16(m, 2H), 6.91(d, $J=8.4$ Hz, 1H), 6.17(s, 1H), 4.05(m, 1H), 3.91(s, 3H), 3.90(s, 3H), 3.67(m, 1H), 3.40~3.58(m, 3H), 2.93(m, 1H), 1.92(t, $J=7.2$ Hz, 3H)
	140	8.65(m, 2H), 7.68(d, $J=8.1$ Hz, 1H), 7.54(s, 1H), 7.37(m, 1H), 7.09(d, $J=8.4$ Hz, 1H), 7.04(s, 1H), 6.90(d, $J=8.4$ Hz, 1H), 5.96(s, 1H), 4.30(m, 1H), 4.17(m, 2H), 3.91(s, 3H), 3.90(s, 3H), 3.05(m, 1H), 2.05(s, 3H)
10	141	8.66(brs, 2H), 7.69(m, 1H), 7.52(s, 1H), 7.36(m, 1H), 7.08(dd, $J=8.4$, 1.8Hz, 1H), 7.04(d, $J=1.8$ Hz, 1H), 6.90(d, $J=8.4$ Hz, 1H), 6.05(s, 1H), 4.14(q, $J=7.2$ Hz, 2H), 3.91(m, 1H), 3.90(s, 3H), 3.89(s, 3H), 3.19(m, 1H), 2.82(m, 1H), 2.50(m, 1H), 1.25(t, $J=7.2$ Hz, 3H)
15	145	8.71(m, 1H), 8.61(m, 1H), 7.73(m, 1H), 7.50(s, 1H), 7.33(m, 1H), 7.09(d, $J=8.4$ Hz, 1H), 7.05(s, 1H), 6.90(d, $J=8.4$ Hz, 1H), 6.27(s, 1H), 3.90(s, 3H), 3.89(s, 3H), 3.78(m, 1H), 3.35(m, 1H), 3.00(m, 1H), 2.97(s, 3H), 2.94(s, 3H), 2.50(m, 1H)
20	146	DMSO-d ₆ ; 8.64(m, 1H), 8.60(m, 1H), 7.75(m, 1H), 7.44(m, 1H), 7.41(s, 1H), 7.12~7.05(m, 3H), 6.32(s, 1H), 3.78(s, 3H), 3.77(s, 3H), 3.30~3.21(m, 5H), 3.05(m, 1H), 2.67(m, 1H), 2.39(m, 1H), 1.77(m, 4H)
	148	8.62(m, 2H), 7.65(m, 1H), 7.38(m, 1H), 7.23(d, $J=11.1$ Hz, 1H), 6.98(d, $J=8.4$ Hz, 1H), 6.92(s, 1H), 6.85(d, $J=8.4$ Hz, 1H), 6.75(d, $J=15.3$ Hz, 1H), 6.58(dd, $J=15.3$, 11.1Hz, 1H), 6.15(s, 1H), 3.92(m, 1H), 3.91(s, 3H), 2.83(m, 1H), 2.59(m, 1H), 2.28(m, 1H), 2.20(s, 6H)
25		

Comp. No.	¹ H NMR(300 MHz) δ
5	149 8.60(m, 2H), 7.70(d, $J=7.6$ Hz, 1H), 7.67(s, 1H), 7.39(dd, $J=7.6, 4.2$ Hz, 1H), 7.14(d, $J=11.1$ Hz, 1H), 6.97(s, 1H), 6.78(s, 2H), 6.70(d, $J=15.3$ Hz, 1H), 6.48(dd, $J=15.3, 11.1$ Hz, 1H), 6.17(s, 1H), 3.90(m, 1H), 2.80(m, 1H), 2.50(m, 1H), 2.35(m, 1H), 2.17(s, 6H)
	150 8.64~8.59(m, 2H), 7.69~7.66(m, 1H), 7.37~7.33(m, 1H), 7.22(d, $J=11.1$ Hz, 1H), 7.09(s, 2H), 6.72(d, $J=15.3$ Hz, 1H), 6.55(dd, $J=15.3, 11.1$ Hz, 1H), 3.98~3.90(m, 1H), 2.86~2.77(m, 1H), 2.60~2.51(m, 1H), 2.37~2.28(m, 1H), 2.24(s, 6H), 2.18(s, 6H)
10	151 8.63(m, 2H), 7.67(m, 1H), 7.36(m, 1H), 7.23(d, $J=11.1$ Hz, 1H), 6.75(d, $J=15.6$ Hz, 1H), 6.68(s, 2H), 6.59(dd, $J=15.6, 11.2$ Hz, 1H), 6.16(s, 1H), 3.97(m, 1H), 3.91(s, 6H), 2.84(m, 1H), 2.55(m, 1H), 2.35(m, 1H), 2.18(s, 6H)
15	152 8.62(m, 2H), 7.69(m, 1H), 7.41(m, 1H), 7.23(s, 2H), 7.08(d, $J=11.2$ Hz, 1H), 6.91(d, $J=15.2$ Hz, 1H), 6.53(dd, $J=15.2, 11.2$ Hz, 1H), 6.24(s, 1H), 5.37(s, 1H), 3.94(m, 1H), 2.82(m, 1H), 2.57(m, 1H), 3.31(m, 2H), 2.31(m, 1H), 2.18(s, 6H), 1.21(d, $J=7.2$ Hz, 12H)
20	153 8.61(m, 2H), 7.69(dt, $J=7.8, 1.8$ Hz, 1H), 7.38(m, 1H), 7.25(s, 2H), 7.09(d, $J=11.1$ Hz, 1H), 6.92(d, $J=15$ Hz, 1H), 6.54(dd, $J=15.0, 11.1$ Hz, 1H), 6.25(s, 1H), 5.37(s, 1H), 3.92(m, 1H), 2.82(m, 1H), 2.56(m, 1H), 2.31(m, 1H), 2.18(s, 6H), 1.45(s, 18H)

Comp. No.	¹ H NMR(300 MHz) δ
5	158 8.62(m, 2H), 7.65(m, 1H), 7.38(m, 1H), 7.23(d, $J=11.1$ Hz, 1H), 7.11(m, 10H), 6.98(d, $J=8.4$ Hz, 1H), 6.92(s, 1H), 6.85(d, $J=8.4$ Hz, 1H), 6.75(d, $J=15.2$ Hz, 1H), 6.58(dd, $J=15.2, 11.1$ Hz, 1H), 6.25(s, 1H), 4.25(s, 1H), 3.92(m, 1H), 3.91(s, 3H), 2.83(m, 3H), 2.65(m, 8H)
10	159 8.62(m, 2H), 7.58(m, 1H), 7.42(m, 1H), 7.24(d, $J=11.2$ Hz, 1H), 6.97(d, $J=8.4$ Hz, 1H), 6.91(s, 1H), 6.82(d, $J=8.4$ Hz, 1H), 6.72(d, $J=15.3$ Hz, 1H), 6.55(dd, $J=15.3, 11.2$ Hz, 1H), 6.20(s, 1H), 3.95(m, 1H), 3.92(s, 3H), 2.83(m, 1H), 2.59(m, 6H), 1.82(m, 4H), 0.98(m, 2H)
15	160 8.64(m, 2H), 7.62(m, 1H), 7.40(m, 1H), 7.24(d, $J=11.1$ Hz, 1H), 6.98(d, $J=8.4$ Hz, 1H), 6.92(s, 1H), 6.85(d, $J=8.4$ Hz, 1H), 6.76(d, $J=15.3$ Hz, 1H), 6.57(dd, $J=15.3, 11.1$ Hz, 1H), 6.15(s, 1H), 3.95(m, 5H), 3.91(s, 3H), 3.62(m, 5H), 2.83(m, 1H), 2.59(m, 1H)
20	161 8.61(m, 2H), 7.68(m, 1H), 7.34(m, 1H), 7.22(d, $J=11.1$ Hz, 1H), 6.71(d, $J=15.6$ Hz, 1H), 6.68(s, 2H), 6.57(dd, $J=15.6, 11.1$ Hz, 1H), 5.93(s, 1H), 3.92(s, 6H), 3.82(m, 1H), 2.86(m, 1H), 2.20~2.40(m, 2H), 2.24(s, 6H), 1.50~1.90(m, 2H) 162 8.63(m, 2H), 7.69(m, 1H), 7.35(m, 1H), 7.23(d, $J=11.2$ Hz, 1H), 6.98(d, $J=8.2$ Hz, 1H), 6.93(s, 1H), 6.87(d, $J=8.2$ Hz, 1H), 6.73(d, $J=15.6$ Hz, 1H), 6.57(dd, $J=15.6, 11.2$ Hz, 1H), 5.90(s, 1H), 3.92(s, 3H), 3.79(m, 1H), 2.88(m, 1H), 2.26(m, 2H), 2.20(s, 6H), 1.55~1.95(m, 2H)

Comp. No.		¹ H NMR(300 MHz) δ
5	163	8.62(m, 2H), 7.65(m, 1H), 7.45(d, $J=12.0$ Hz, 1H), 7.33(m, 1H), 6.98(d, $J=8.4$ Hz, 1H), 6.85(d, $J=8.4$ Hz, 1H), 6.73(s, 1H), 6.18(d, $J=12$ Hz, 1H), 6.12(s, 1H), 4.15(m, 1H), 3.89(s, 3H), 2.79(m, 5H), 2.51(m, 4H), 1.74(m, 4H), 1.07(t, $J=7.6$ Hz, 3H)
	164	8.64(m, 2H), 7.75(m, 1H), 7.33(m, 1H), 7.25(m, 2H), 6.92(t, $J=8.4$ Hz, 1H), 6.82(m, 4H), 6.49(t, 1H), 6.12(s, 1H), 3.89(m, 1H), 3.79(s, 3H), 3.76(s, 3H), 2.82(m, 1H), 2.52(m, 1H), 2.31(m, 1H), 2.16(s, 6H)
10	165	8.63(m, 1H), 8.59(m, 1H), 7.66(m, 1H), 7.36(m, 1H), 7.23(d, $J=11.1$ Hz, 1H), 6.75(d, $J=15.3$ Hz, 1H), 6.67(s, 2H), 6.56(dd, $J=15.3, 11.1$ Hz, 1H), 6.17(s, 1H), 3.98(m, 1H), 3.91(s, 6H), 2.84(m, 2H), 2.45(m, 5H), 1.76(m, 4H)
15	166	8.64(m, 1H), 8.59(m, 1H), 7.66(m, 1H), 7.37(m, 1H), 7.22(d, $J=10.5$ Hz, 1H), 7.14(s, 2H), 6.60~6.80(m, 2H), 6.22(s, 1H), 4.32(q, $J=7.2$ Hz, 2H), 3.85(m, 1H), 2.68~2.92(m, 2H), 2.16~2.63(m, 5H), 2.20(s, 6H), 1.38(t, $J=7.2$ Hz, 3H), 0.99(t, $J=7.2$ Hz, 6H)
20	168	8.61(m, 2H), 7.66(m, 1H), 7.45(d, $J=12$ H, 1H), 7.34(m, 1H), 6.98(d, $J=8.4$ Hz, 1H), 6.89(d, $J=8.4$ Hz, 1H), 6.73(s, 1H), 6.19(d, $J=12$ Hz, 1H), 6.13(s, 1H), 3.90(s, 3H), 3.89(m, 1H), 2.76(m, 3H), 2.57(m, 1H), 2.21(m, 1H), 2.18(s, 6H), 1.22(t, $J=7.6$ Hz, 3H)
	169	8.63(m, 1H), 8.57(m, 1H), 7.64(m, 1H), 7.38(m, 1H), 7.19(d, $J=11.4$ Hz, 1H), 6.95(d, $J=8.4$ Hz, 1H), 6.91(s, 1H), 6.83(d, $J=8.4$ Hz, 1H), 6.73(d, $J=15.3$ Hz, 1H), 6.52(dd, $J=15.3, 11.4$ Hz, 1H), 6.15(s, 1H), 4.05(m, 1H), 3.90(s, 3H), 2.82(m, 2H), 2.45(m, 5H), 1.76(m, 4H)
25		

Comp. No.		¹ H NMR(300 MHz) δ
5	170	8.63(m, 1H), 8.60(m, 1H), 7.68(m, 1H), 7.37(m, 1H), 7.23(d, $J=11.1$ Hz, 1H), 7.08(s, 2H), 6.72(d, $J=15.3$ Hz, 1H), 6.56(dd, $J=15.3, 11.1$ Hz, 1H), 6.14(s, 1H), 3.96(m, 1H), 2.83(m, 2H), 2.44(m, 4H), 2.24(s, 6H), 1.75(m, 4H)
	171	8.63(m, 1H), 8.59(m, 1H), 7.66(m, 1H), 7.35(m, 1H), 7.22(d, $J=10.8$ Hz, 1H), 7.09(s, 2H), 6.72(d, $J=15.2$ Hz, 1H), 6.58(dd, $J=15.2, 10.8$ Hz, 1H), 6.20(s, 1H), 3.84(m, 1H), 2.68-2.92(m, 2H), 2.33-2.60(m, 6H), 2.24(s, 6H), 0.99(t, $J=7.2$ Hz, 6H)
10	173	8.64(m, 1H), 8.59(m, 1H), 7.66(m, 1H), 7.36(m, 1H), 7.21(d, $J=11.2$ Hz, 1H), 6.93(d, $J=8.2$ Hz, 1H), 6.93(s, 1H), 6.86(d, $J=8.2$ Hz, 1H), 6.75(d, $J=15.2$ Hz, 1H), 6.57(dd, $J=15.2, 11.2$ Hz, 1H), 6.22(s, 1H), 3.91(s, 3H), 3.85(m, 1H), 2.82(m, 2H), 2.52(m, 5H), 0.99(t, $J=7.2$ Hz, 6H)
	175	8.65-8.61(m, 2H), 7.68(m, 1H), 7.35(m, 1H), 7.21(d, $J=11.1$ Hz, 1H), 7.10(s, 2H), 6.72(d, $J=15.3$ Hz, 1H), 6.55(dd, $J=15.3, 11.1$ Hz, 1H), 3.99(m, 1H), 6.21(s, 1H), 4.32(q, $J=7.6$ Hz, 2H), 2.83(m, 1H), 2.65(m, 1H), 2.30(m, 1H), 2.24(s, 6H), 2.19(s, 6H), 1.25(t, $J=7.6$ Hz, 3H)
20	176	8.64(m, 1H), 8.61(m, 1H), 7.65(m, 1H), 7.36(m, 1H), 7.22(d, $J=10.5$ Hz, 1H), 7.14(s, 1H), 6.75(d, $J=14.3$ Hz, 1H), 6.64(dd, $J=14.3, 10.5$ Hz, 1H), 6.16(s, 1H), 4.32(q, $J=6.9$ Hz, 2H), 3.99(m, 1H), 2.83(m, 2H), 2.43(m, 5H), 2.19(s, 6H), 1.75(m, 4H), 1.38(t, $J=6.9$ Hz, 3H)

Comp. No.	¹ H NMR(300 MHz) δ
5	177 8.64~8.59(m, 2H), 7.70(m, 1H), 7.35(m, 1H), 7.23(d, $J=14.7$ Hz, 1H), 7.21(s, 1H), 7.14(s, 1H), 6.77(d, $J=16.5$ Hz, 1H), 6.51(dd, $J=16.5$, 14.7Hz, 1H), 6.13(s, 1H), 3.94(m, 1H), 2.82(m, 1H), 2.55(m, 1H), 2.33(m, 1H), 2.48(s, 3H), 2.18(s, 6H), 1.41(s, 9H)
	178 8.61(m, 2H), 7.67(m, 1H), 7.34(m, 1H), 7.27(d, $J=10.8$ Hz, 1H), 7.18(s, 1H), 7.10(d, $J=15$ Hz, 1H), 6.48(dd, $J=15$, 10.8Hz, 1H), 6.14(s, 1H), 3.95(m, 1H), 2.82(m, 1H), 2.58(m, 1H), 2.40(m, 1H), 2.26(s, 3H), 2.22(s, 3H), 2.21(s, 3H), 2.18(s, 6H)
10	179 8.64(m, 1H), 8.58(m, 1H), 7.68(m, 1H), 7.36(m, 1H), 7.27(d, $J=11.2$ Hz, 1H), 6.89(d, $J=15.6$ Hz, 1H), 6.50(s, 1H), 6.17(dd, $J=15.6$, 11.2Hz, 1H), 6.12(s, 1H), 3.95(m, 1H), 2.80(m, 1H), 2.50(m, 1H), 2.30(m, 1H), 2.24(s, 3H), 2.28(s, 3H), 2.18(s, 6H), 2.15(s, 3H)
15	180 8.53~8.47(m, 2H), 7.64~7.73(m, 1H), 7.36(dd, $J=7.8$, 4.8Hz, 1H), 7.21(s, 1H), 7.02~7.12(m, 2H), 6.64~6.71(m, 1H), 6.63(s, 1H), 6.40(dd, $J=15.3$, 11.1Hz, 1H), 6.11(s, 1H), 3.96~4.08(m, 1H), 2.72~2.87(m, 1H), 2.49~2.60(m, 1H), 2.36~2.49(m, 1H), 2.25(s, 9H)
	181 8.65(m, 1H), 8.60(m, 1H), 7.68(m, 1H), 7.44(m, 2H), 7.22~7.41(m, 4H), 6.65~6.92(m, 2H), 6.16(s, 1H), 3.94(m, 1H), 2.82(m, 1H), 2.53(m, 1H), 2.32(m, 1H), 2.17(s, 6H)
20	182 8.60~8.65(m, 2H), 7.67~7.69(m, 1H), 7.35~7.41(m, 1H), 7.24(d, $J=11.4$ Hz, 1H), 7.00(d, $J=8.1$ Hz), 6.82(d, $J=8.1$ Hz, 1H), 6.78(d, $J=15.1$ Hz), 6.59(dd, $J=15.1$, 11.4Hz, 1H), 6.15(s, 1H), 3.93(m, 1H), 3.91(s, 3H), 3.90(s, 3H), 2.84(m, 1H), 2.58(m, 1H), 2.33(m, 1H), 2.20(s, 6H)
25	

Comp. No.	¹ H NMR(300 MHz) δ
5	183 9.10(brs, 1H), 8.62(m, 2H), 7.67(m, 1H), 7.38(m, 1H), 7.30(d, $J=8.4$ Hz, 2H), 7.19(d, $J=11.2$ Hz, 1H), 6.81(d, $J=8.4$ Hz, 2H), 6.76(d, $J=15.0$ Hz, 1H), 6.53(dd, $J=15.0, 11.2$ Hz, 1H), 6.15(s, 1H), 3.91(m, 1H), 2.83(m, 1H), 2.54(m, 1H), 2.32(m, 1H), 2.18(s, 6H)
10	184 8.65(dd, $J=4.8, 1.5$ Hz, 1H), 8.60(d, $J=2.1$ Hz, 1H), 7.68(td, $J=7.8, 1.8$ Hz, 1H), 7.40(m, 1H), 7.24(d, $J=11.4$ Hz, 1H), 7.01(dd, $J=8.1, 1.5$ Hz, 1H), 6.93(d, $J=1.5$ Hz, 1H), 6.88(d, $J=8.1$ Hz, 1H), 6.78(d, $J=15.3$ Hz, 1H), 6.55(dd, $J=15.3, 11.4$ Hz, 1H), 5.70(s, 1H), 3.92(s, 3H), 2.87(s, 3H)
15	185 8.55(m, 2H), 7.60(m, 1H), 7.29(m, 1H), 7.10(d, $J=11.4$ Hz, 1H), 6.97(m, 2H), 6.93(m, 1H), 6.87(d, $J=8.4$ Hz, 1H), 6.71(d, $J=15.3$ Hz, 1H), 6.51(dd, $J=15.3, 11.4$ Hz, 1H), 5.74(s, 1H), 4.96(dd, $J=9.0, 3.6$ Hz, 1H), 3.94(s, 3H), 3.46(dd, $J=13.5, 3.6$ Hz, 1H), 3.17(s, 3H), 2.90(dd, $J=13.5, 9.0$ Hz, 1H)
20	188 8.46(m, 2H), 7.51(m, 1H), 7.24(m, 1H), 7.14(d, $J=11.1$ Hz, 1H), 7.02(m, 1H), 6.95(s, 1H), 6.88(d, $J=8.1$ Hz, 1H), 6.73(d, $J=15.3$ Hz, 1H), 6.59(dd, $J=15.3, 11.1$ Hz, 1H), 5.81(s, 1H), 4.80(m, 1H), 3.94(s, 3H), 2.99(s, 3H), 2.69(m, 2H), 2.01(m, 1H), 1.82(m, 2H), 1.67(m, 1H)
	189 8.47(d, $J=3.3$ Hz, 1H), 7.46(d, $J=7.8$ Hz, 1H), 7.20(m, 2H), 7.07(s, 2H), 6.70(d, $J=15.3$ Hz, 1H), 6.50(dd, $J=15.3, 11.1$ Hz, 1H), 4.02(m, 1H), 2.80(m, 1H), 2.62(s, 3H), 2.59(m, 1H), 2.3(m, 1H), 2.34(s, 6H), 2.15(s, 6H)

Comp. No.	¹ H NMR(300 MHz) δ
5	190 8.47(m, 1H), 7.46(m, 1H), 7.20(m, 2H), 7.07(s, 2H), 6.68(d, $J=15.3$ Hz, 1H), 6.50(dd, $J=15.3, 11.1$ Hz, 1H), 4.31(q, $J=7.6$ Hz, 2H), 4.02(m, 1H), 2.80(m, 1H), 2.62(s, 3H), 2.59(m, 1H), 2.30(m, 1H), 2.34(s, 6H), 2.15(s, 6H), 1.25(t, $J=7.6$ Hz, 3H)
10	193 8.64(m, 1H), 8.60(m, 1H), 7.77(m, 1H), 7.35(m, 1H), 7.24(d, $J=11.1$ Hz, 1H), 7.08~7.00(m, 3H), 6.81(d, $J=15.3$ Hz, 1H), 6.67(dd, $J=15.3, 11.1$ Hz, 1H), 6.16(s, 1H), 4.31(q, $J=7.2$ Hz, 2H), 3.94(m, 1H), 3.87(s, 3H), 2.82(m, 1H), 2.56(m, 1H), 2.31(m, 1H), 2.17(s, 6H), 1.38(t, $J=7.2$ Hz, 3H)
15	194 8.63~8.58(m, 2H), 7.66(m, 1H), 7.35(m, 1H), 7.24(s, 1H), 6.96(s, 2H), 6.65(s, 1H), 6.07(s, 1H), 3.95(m, 1H), 2.83(m, 1H), 2.55(m, 1H), 2.30(m, 1H), 2.24(s, 6H), 2.17(s, 6H), 2.15(s, 3H)
	195 8.63(m, 2H), 7.69(m, 1H), 7.34(m, 1H), 7.19(s, 1H), 6.95(s, 2H), 6.61(s, 1H), 6.08(s, 1H), 3.95(m, 1H), 2.85(m, 1H), 2.60~2.30(m, 2H), 2.95(m, 1H), 2.24(s, 6H), 2.17(s, 6H), 1.18(t, $J=7.6$ Hz, 3H)
20	196 8.63~8.58(m, 2H), 7.68(m, 1H), 7.35(m, 1H), 7.20(s, 1H), 6.93(s, 2H), 6.63(s, 1H), 6.07(s, 1H), 3.90(m, 1H), 2.85(m, 1H), 2.60~2.20(m, 4H), 2.24(s, 6H), 2.17(s, 6H), 1.69~1.22(m, 2H), 0.96(t, $J=8.7$ Hz, 3H)
25	197 8.57~8.67(m, 2H), 7.62~7.73(m, 1H), 7.31~7.40(m, 1H), 7.26(d, $J=2.7$ Hz, 1H), 6.82~6.96(m, 2H), 6.73(s, 1H), 6.08(s, 1H), 5.29(s, 1H), 3.90~4.05(m, 1H), 3.89(s, 3H), 3.88(s, 3H), 2.77~2.93(m, 1H), 2.48~2.64(m, 1H), 2.27~2.40(m, 1H), 2.19(s, 6H), 2.22(d, $J=0.9$ Hz, 3H)

Comp. No.	¹ H NMR(300 MHz) δ
5	198 8.58~8.64(m, 2H), 7.65~7.68(m, 1H), 7.34~7.37(m, 1H), 7.24(d, $J=7.5$ Hz, 1H), 6.80~6.87(m, 4H), 6.69(s, 1H), 6.07(s, 1H), 3.98~4.01 (m, 1H), 3.88(s, 3H), 2.77~2.92(m, 1H), 2.48~2.64(m, 1H), 2.27~2.39 (m, 1H), 0.21(s, 3H), 2.19(s, 6H)
10	199 8.59(m, 2H), 7.62(m, 1H), 7.38(m, 1H), 7.20(s, 1H), 6.87(m, 2H), 6.85(s, 1H), 6.09(s, 1H), 5.29(s, 1H), 3.88(s, 3H), 3.85(m, 1H), 2.85(m, 1H), 2.52(m, 3H), 2.25(m, 1H), 2.17(s, 6H), 1.27(t, $J=6.8$ Hz, 3H)
15	200 8.62(m, 2H), 7.64(m, 1H), 7.38(m, 1H), 7.19(s, 1H), 6.83(m, 3H), 6.66(s, 1H), 6.08(s, 1H), 3.98(m, 1H), 3.87(s, 3H), 2.85(m, 1H), 2.47(m, 4H), 2.19(s, 6H), 1.65(m, 2H), 0.94(t, $J=6.8$ Hz, 3H)
20	207 8.60(m, 2H), 7.68(m, 1H), 7.35(m, 1H), 7.20(s, 1H), 6.65(s, 1H), 6.55 (s, 2H), 6.10(s, 1H), 3.95(m, 1H), 3.87(s, 6H), 2.85(m, 1H), 2.30~2.60 (m, 4H), 2.18(s, 6H), 1.21(t, $J=7.6$ Hz, 3H)
20	208 8.62(m, 2H), 7.65(m, 1H), 7.38(m, 1H), 7.20(s, 1H), 6.65(s, 1H), 6.55(s, 2H), 6.10(s, 1H), 3.97(m, 1H), 3.88(s, 6H), 2.80(m, 1H), 2.54(m, 2H), 2.35(m, 2H), 2.19(s, 6H), 1.23(t, $J=7.6$ Hz, 3H)
20	211 8.63(d, $J=4.3$ Hz, 1H), 8.59(d, $J=1.8$ Hz, 1H), 7.62~7.73(m, 1H), 7.36 dd, $J=7.8, 4.8$ Hz, 1H), 7.13(d, $J=7.8$ Hz, 1H), 7.06(s, 2H), 6.59(m, 3H), 6.21 (dd, $J=13.8, 11.7$ Hz, 1H), 6.13(s, 1H), 3.98(m, 1H), 2.82(m, 1H), 2.59 (m, 1H), 2.38(m, 1H), 2.23(s, 6H), 2.17(s, 6H)

25 The present invention further relates to pharmaceutical compositions containing these compounds or acceptable salts thereof and the use of these compounds as antagonist of the PAF and/or inhibitor of the leukotriene. As stated above, compounds of the present invention possess activity of PAF-antagonist and/or

leukotriene-inhibition. Thus compounds of the invention may be used for the treatment and prophylaxis of diseases mediated or effected by PAF and leukotriene.

The typical diseases for which the compounds of the present invention may be used as a therapeutic and prophylactic agent include inflammation (for example, arthritis, nephritis), circulatory diseases (for example, shock, thrombosis, transplant rejection, cerebral anemia, etc.) and allergic diseases (for example, asthma, psoriasis).

The compounds according to the invention, as well as the pharmaceutically acceptable salts thereof, have potent PAF-antagonistic and leukotriene-inhibitory activity. Accordingly the novel compounds may be used in pharmaceutical composition comprising a pharmaceutically effective amount of one of the compounds defined above and a pharmaceutically acceptable carrier. The inventive compounds are particularly useful as anti-allergic agents, anti-asthmatic agents, anti-psoriasis agents, anti-anaphylactic shock agents, anti-septic shock agents, anti-arthritis agents, anti-nephritic agents, anti-thromboplastic agents, anti-transplant rejection agents and anti-cerebral anemic agents.

The compounds according to the present invention, as well as the pharmaceutically acceptable salt thereof, may be incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutically acceptable carriers may also be employed. Solid carriers include starch, lactose, calcium sulphate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline solution and water.

The carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with wax. When a liquid carrier is used, the preparation may be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid (e.g. solution) or a nonaqueous or aqueous liquid suspension.

The pharmaceutical preparations are prepared conventional techniques of the

pharmaceutical chemist.

Compounds according to the present invention may be administrated orally topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and
5 vehicles.

The term parenteral as used herein includes subcutaneous injections, intravenous injection, intramuscular injection, intrasternal injection or infusion techniques.

An exemplary daily dosage employed depends on the type of disease, the
10 degree of symptom and age. The dosage levels of the compound in the above-indicated compositions may, of course, be varied and may conveniently be between about 0.01mg to about 2(X) mg per kilogram of the weight.

Pharmaceutical compositions containing compounds according to the invention may be in any form suitable for oral use, for example, as tablets, troches, lozenges,
15 aqueous or oily suspensions, dispensable powders or granules, emulsion, hard or soft capsules, syrups or elixirs.

The tablets, capsules and the like may also contain a binder such as, e.g., lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose or gelatin; excipients such as, e.g., dicalcium phosphate; a disintegrating agent such as, e.g., corn
20 starch or potato starch; a lubricant such as, e.g., magnesium stearate, calcium stearate, sodium stearylmalate or polyethylene glycol wax. When the dosage unit form is a capsule, it may further contain, in addition to the types of materials described above, a liquid carrier such as e.g., a fatty oil.

These active compounds according to the present invention may also be
25 administered parenterally. A solution or suspension of the active compounds may be prepared in water, optionally mixed with stabilizer or buffering agents. The dosages for parenteral administration are preferably as ampule or vial type.

These active compounds according to the invention may also be administered

by any known process of administrating the dose including topically, for example, an ointment, cream, jelly, solution, suspension or pachydematous patch; rectally, for example, suppository; intranasally or intrathoracally by inhalation spray.

Accordingly, the present invention provides pharmaceutical compositions comprising a pharmaceutically effective amount of thiazolidin-4-one derivatives and a pharmaceutically acceptable salt thereof. The present invention also provides the pharmaceutical uses of these compounds and compositions, especially for the prevent or treatment of various PAF- and/or leukotriene- induced diseases.

[pharmaceutical compositions]

10 Orally administration(Tablet) :

Composition	mg/Tablet	mg/Tablet
Active Ingredient	100	500
Lactose	122	113
Corn starch/water	30	40
15 Corn starch	45	40
Magnesium stearate	3	7
Total	300	700

Parenteral administration :

Composition	mg/vial	mg/vial
sterile active ingredient powder	100	500

※ Sterile water may be added to the above composition for intravenous injection.

25 The compounds of this invention were tested for pharmacological activity as described in the following pharmacology examples.

Pharmacology Example 1 : PAF-induced rabbit platelet aggregation.

Blood was collected from the ear artery of a male New Zealand white rabbit and mixed with 3.8 % sodium citrate in a 9:1 volume ratio. Platelet rich plasma (PRP) was obtained by centrifugation of blood at 150 g for 10 min at room temperature. The number of platelets was adjusted to 3×10^8 platelets/mL with platelet poor plasma. Platelet aggregation was monitored by continuous recording of light transmission in a dual-channel aggregometer (Chrono-Log 560-VS) coupled with a two channel recorder (Chrono-Log 707). Stirred PRP was treated with various concentration of test compounds or vehicle (0.5 % DMSO) for 2 min and then PAF (5×10^{-9} M) was added to induce platelet aggregation.

Inhibition values were calculated by comparing the extent of aggregation obtained in the presence of the vehicle alone (0.5 % DMSO) and in the presence of a test compound. Log concentration-response curves were generated and the IC_{50} values were determined by regression analysis.

Pharmacology Example 2 : Inhibitory activity for LTB_4 biosynthesis

A suspension of rat basophilic leukemia-1 cell in phosphoric acid buffer solution with a concentration of 5×10^6 /mL was allowed at 37°C for 5 min and added the compound of thiazolidin-4-one. After allowed for 5 min, to the mixture was added arachidonic acid (25 μg /mL) and calcium ionophore A23187 (1 μg /mL). After allowed for 15 min, the reaction mixture was quenched with 0.1N cooled hydrochloric acid and centrifuged with 3,300 rpm for 5 min. The supernatant solution was extracted with ethyl acetate and concentrated under nitrogen gas. The residue was dissolved in mobile phase and a amount of LTB_4 was determined with HPLC.

Table 7 lists result from this assay for inhibition of PAF-induced rabbit platelet aggregation and of LTB_4 biosynthesis for illustrative examples of the compounds of this invention.

Table 7 : Inhibitory activity of PAF-induced rabbit platelet aggregation and LTB₄ biosynthesis

5	Compound	PAF IC ₅₀	Inhibition of LTB ₄ biosynthesis
	No.	(μ M)	(%, 10 μ M)
5	1	1.741	30
	2	0.058	47
	3	0.079	54
	4	0.211	67
10	6	1.901	85
	7	0.065	74
	8	1.348	45
	9	15.21	63
15	10	0.535	92
	11	0.496	89
	12	0.141	42
	13	0.329	37
20	14	4.21	75
	15	2.101	47
	16	3.21	25
	17	0.721	43
25	18	0.071	62
	19	0.046	65
	20	3.37	43
	21	1.021	89

	Compound	PAF IC ₅₀	Inhibition of LTB ₄ biosynthesis
	No.	(μ M)	(%, 10 μ M)
5	22	0.274	41
	23	0.058	57
	38	2.123	92
	39	7.21	99
	40	0.501	42
	63	0.258	39
10	64	0.526	47
	67	3.21	100
	68	1.37	100
	69	1.21	65
	70	4.74	75
	71	2.53	67
15	72	4.21	17
	73	5.22	100
	74	4.72	100
	78	3.73	45
	79	6.73	100
	80	7.21	65
20	81	25.7	25
	82	4.21	30

	Compound	PAF IC ₅₀	Inhibition of LTB ₄ biosynthesis
	No.	(μ M)	(%, 10 μ M)
5	83	12.7	36
	84	25.8	100
	85	12.1	35
	86	15.7	40
	87	25.1	50
10	88	30.2	48
	89	22.7	100
	90	4.21	42
	91	13.72	65
	92	12.71	38
15	93	12.71	43
	94	27.2	17
	95	11.7	49
	96	10.5	37
	97	13.5	27
20	98	12.8	42
	99	12.5	52
	100	13.7	100
	101	14.2	42
	102	12.6	37

	Compound	PAF IC ₅₀	Inhibition of LTB ₄ biosynthesis
	No.	(μ M)	(%, 10 μ M)
5	103	13.8	100
	104	14.7	48
	105	12.7	47
	106	21.6	38
	107	9.76	63
10	108	12.1	63
	109	13.6	57
	110	12.7	37
	111	12.4	100
	112	11.3	67
15	115	12.5	28
	116	13.7	98
	117	13.4	42
	118	15.4	98
	119	9.78	45
20	120	7.21	100
	121	8.47	72
	122	8.52	100
	123	27.2	52
	124	25.7	100

	Compound	PAF IC ₅₀	Inhibition of LTB ₄ biosynthesis
	No.	(μ M)	(%, 10 μ M)
5	125	23.2	60
	126	21.8	95
	127	23.7	100
	128	20.5	47
	129	18.7	62
10	130	12.5	20
	131	14.2	95
	132	12.7	72
	133	13.5	25
	138	15.8	32
15	139	14.8	27
	140	15.6	42
	148	0.046	82
	149	1.21	93
	150	0.023	100
20	151	2.32	85
	152	0.125	52
	153	0.577	42
	158	4.21	100
	159	6.38	92

	Compound	PAF IC ₅₀	Inhibition of LTB ₄ biosynthesis
	No.	(μ M)	(%, 10 μ M)
5	161	9.82	60
	162	3.71	59
	163	0.087	40
	164	0.227	45
	165	4.82	75
10	169	0.115	63
	170	0.025	100
	171	0.050	100
	173	1.25	65
	175	0.018	100
15	176	0.020	100
	178	0.059	50
	179	0.194	10
	182	0.155	30
	184	7.8	100
20	185	8.2	100
	189	0.012	100
	190	0.010	100
	191	0.015	100
	193	0.042	80

	Compound	PAF IC ₅₀	Inhibition of LTB ₄ biosynthesis
	No.	(μ M)	(%, 10 μ M)
5	194	0.010	100
	195	0.042	80
	198	0.116	54
	201	0.012	100
	204	0.010	100
10	205	0.005	100
	209	0.002	100
	211	0.132	100
	212	1.25	100

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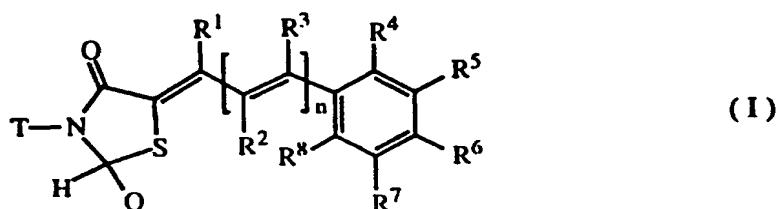
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WHAT IS CLAIMED IS :

1. A compound of the following formula(I) or a pharmaceutically acceptable salt thereof

5



wherein,

n is 0, 1, 2 or 3;

10 Q is $C_1 - C_{10}$ alkyl group, phenyl group that is optionally substituted with one or more suitable substituents selected from methoxy group and nitro group, or pyridiyl group that is optionally substituted with one or more methyl group;

15 R^1 , R^2 and R^3 are independently hydrogen atom, $C_1 - C_{10}$ alkyl group, $C_3 - C_6$ cycloalkyl group or phenyl group that is optionally substituted with one or more methoxy group;

20 R^4 , R^5 , R^6 , R^7 and R^8 are independently hydrogen atom, hydroxyl group, halogen atom, $C_1 - C_{10}$ alkyl group, $C_1 - C_{10}$ alkoxy group, nitro group, amino group that is optionally substituted with one or more suitable substituents selected from $C_1 - C_{10}$ alkyl group and $C_3 - C_6$ cycloalkyl group, phenyl group that is optionally substituted with one or more suitable substituents selected from methoxy group and nitro group, $C_1 - C_{10}$ haloalkyl group, $\text{C}_6\text{H}_5-(\text{CH}_2)_m-\text{O}-$,

5

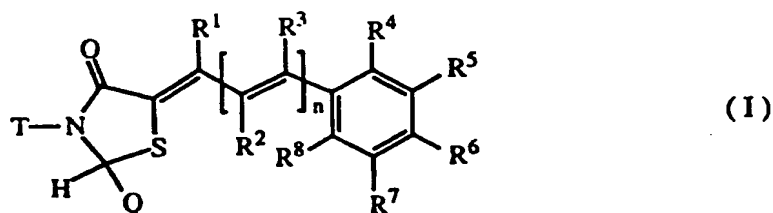
$$\begin{aligned} &-\text{CO}_2\text{H}, \text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3, -\text{OC}(=\text{O})\text{R}^{15}, -\text{OCO}(=\text{O})\text{R}^{15}, -\text{C}(=\text{O})\text{R}^{15}, -\text{C}(=\text{O})\text{NHR}^{15}, \\ &-\text{C}(=\text{O})\text{OR}^{15}, -\text{NHC}(=\text{O})\text{R}^{15}, -\text{CH}_2\text{NH}-\text{R}^{15}, -\text{N}(\text{OH})\text{C}(=\text{O})\text{NHR}^{15}, -\text{C}(=\text{O})\text{N}(\text{OH})\text{R}^{15}, \\ &-\text{NHC}(=\text{O})\text{N}(\text{OH})\text{R}^{15}, -\text{CH}_2\text{NHC}(=\text{O})\text{N}(\text{OH})\text{R}^{15}, -\text{OC}(=\text{O})\text{NR}^{15}\text{R}^{15}, -\text{OC}(\text{R}^{16})_2\text{C}(=\text{O})\text{OR}^{15}, \\ &-\text{OCH}_2\text{O}-\text{C}(=\text{O})\text{R}^{15}, \text{O}-\text{C}(=\text{O})-(\text{CH}_2)_m-\text{C}(=\text{O})\text{OH}, \text{or } -\text{O}-\text{C}(=\text{O})-(\text{CH}_2)_m-\text{C}(=\text{O})\text{OR}^{15} \text{ (in which R}^{15} \text{ is} \\ &\text{C}_1 \sim \text{C}_{10} \text{ alkyl group; and m is 1, 2, 3 or 4); and} \end{aligned}$$

T is hydrogen atom, hydroxyl group, C₁ ~ C₁₀ alkyl group,

10

$$\begin{aligned} &-(\text{CH}_2)_m-\text{R}^9, -(\text{CH}_2)_m-\text{O}-\text{R}^{10}, -(\text{CH}_2)_m-\text{C}(=\text{O})-\text{R}^{11}, \\ &-(\text{CH}_2)_m-\text{NHC}(=\text{O})-\text{R}^{12}, -(\text{CH}_2)_m-\text{N}(\text{OH})\text{C}(=\text{O})-\text{R}^{16}, -(\text{CH}_2)_m-\text{N}(\text{OH})\text{C}(=\text{O})\text{NH}_2, \\ &-(\text{CH}_2)_m-\text{C}(=\text{O})\text{N}(\text{OH})-\text{R}^{16}, \text{ or } -(\text{CH}_2)_m-\text{NR}^{13}\text{R}^{14} \text{ (in which, m is 1, 2, 3} \\ &\text{or 4; R}^9 \text{ is hydrogen atom, phenyl group that is optionally substituted} \\ &\text{with one or more suitable substituents selected from C}_1 \sim \text{C}_6 \text{ alkyl group and} \\ &\text{C}_1 \sim \text{C}_6 \text{ alkoxy group, or a pyridyl group; R}^{10} \text{ is hydrogen atom, C}_1 \sim \text{C}_{10} \\ &\text{15 alkyl group or C}_1 \sim \text{C}_4 \text{ alkanoyl group; R}^{11} \text{ is C}_1 \sim \text{C}_{10} \text{ alkyl group, C}_1 \sim \text{C}_{10} \\ &\text{alkoxy group, or amino group that is optionally substituted with one or more} \\ &\text{suitable substituents selected from C}_1 \sim \text{C}_{10} \text{ alkyl group and C}_3 \sim \text{C}_6 \\ &\text{cycloalkyl group; R}^{12} \text{ is C}_1 \sim \text{C}_{10} \text{ alkyl group or phenyl group; R}^{13} \text{ is} \\ &\text{hydrogen atom, C}_1 \sim \text{C}_{10} \text{ alkyl group, or C}_1 \sim \text{C}_{10} \text{ alkanoyl group; R}^{14} \text{ is} \\ &\text{20 hydrogen atom or C}_1 \sim \text{C}_{10} \text{ alkyl group or when taken together, connecting} \\ &\text{R}^{13} \text{ and R}^{14}, \text{ a substituted or unsubstituted four- to seven-membered} \\ &\text{cycloamino group, or a cycloamino group having another hetero atoms; and} \\ &\text{R}^{16} \text{ is hydrogen atom or C}_1 \sim \text{C}_{10} \text{ alkyl group.} \end{aligned}$$

25 2. A pharmaceutical composition including a compound of the following formula (I) or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier



wherein, n , Q , T , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are respectively as defined in claim 1.

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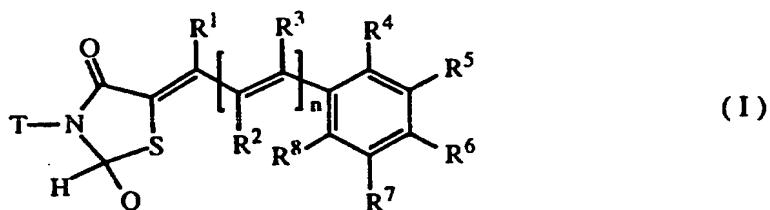
3. A process for treating PAF- and/or leukotriene-induced diseases which comprises the step of administering an effective amount of compound of formula (I) as claimed in claim 1 or pharmaceutically acceptable salt thereof, to a host in need of such treatment.

10

4. The process for treating PAF- and/or leukotriene-induced diseases as claimed in claim 3, the said diseases are arthritis, nephritis, anaphylactic shock, septic shock, thrombosis, transplant rejection, cerebral anemia, asthma or psoriasis.

15

5. A process for preparing compound of the following formula(I) or acceptable salt thereof



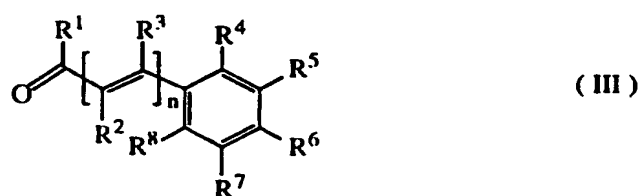
wherein, n , T , Q , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 are respectively as defined in claim 1; reacting compound of the following formula(II)

20



wherein, T and Q are as in defined 1;

with compound of the following formula(III)

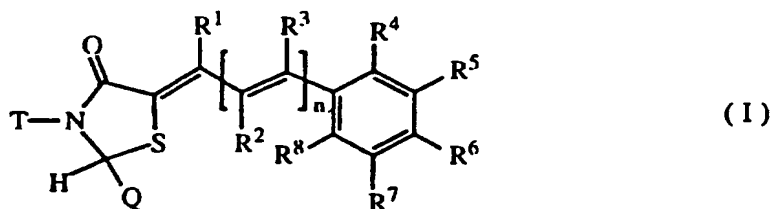


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wherein, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are respectively as defined in claim 1.

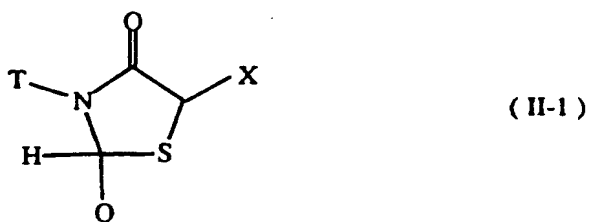
6. A process for preparing compound of the following formula(I) or pharmaceutically acceptable salt thereof

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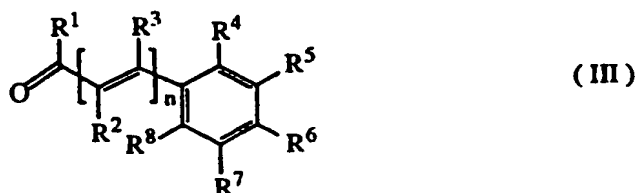
wherein, n, T, Q, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are respectively as defined in claim 1; reacting compound of the following formula(II-1)

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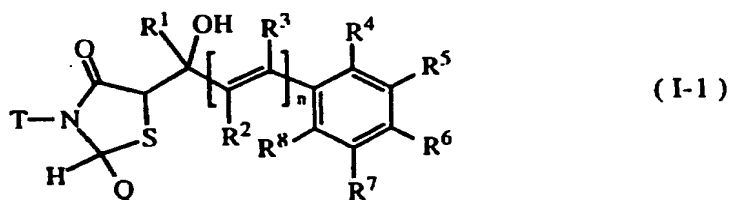
wherein, T and Q are as defined in claim 1, and X is halogen atom;

with compound of the following formula(III)



5 wherein, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are respectively as defined in claim 1;

to obtain compound of the following formula (I-1)

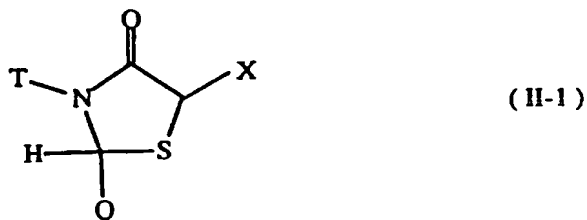


10 wherein, n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are respectively as defined in claim 1; and

reacting the compound of the above formula(I-1) with an acid or alkali.

7. A process for preparing a compound having the following formula(II-1) by

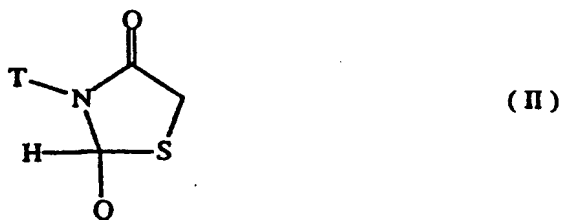
15



wherein, T and Q are as defined in claim 1, and X is halogen atom;

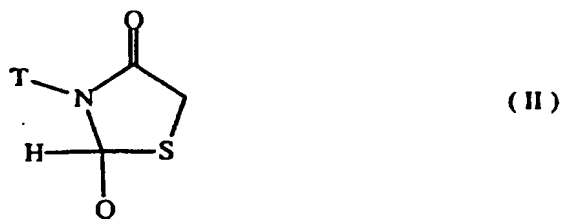
reacting compound of the following formula(II)

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wherein, T and Q are as defined in claim 1;
with halides.

- 5 8. A process for preparing compound of the following formula(II) by



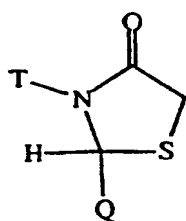
wherein, T and Q are defined as defined in claim 1;
dehydrating compound of Q-CHO (wherein, Q is as defined in claim 1) with
10 compound of T-NH₂ (wherein, T is as defined in claim 1) and mercaptoacetic
acid (HSCH₂CO₂H).

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AMENDED CLAIMS

[received by the International Bureau on 3 May 1996 (03.05.96);
original claim 6 cancelled;
remaining claims unchanged (1 page)].



(II)

wherein, T and Q are as defined in claim 1;
with halides.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 95/00183

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: C 07 D 277/14, 417/04, 417/06, 417/12, 417/14; A 61 K 31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: C 07 D 277/00, 417/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel - DARC, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 292 305 A1 (SUMITOMO) 23 November 1988 (23.11.88), example 63; page 2, lines 6-50; claim 1.	1-4
A	Chemical Abstracts, Vol.112, No.7, 12 February 1990 (Columbus, Ohio, USA), page 772, column 2, abstract No.55851q, ENOMOTO, M. et al.: "Optically active thiazolidin-4-ones as platelet activating factor (PAF) antagonists", Jpn. Kokai Tokkyo Koho JP 01,190,679.	1-4
A	Chemical Abstracts, Vol.96, No.21, 24 May 1982 (Columbus, Ohio, USA), page 704, column 1, abstract No.181185q, DASH, B. et al.: "Thiazolidone derivatives", J. Indian Chem. Soc. 1981, 58(12), 1184-6 (Eng).	1
A	Chemical Abstracts, Vol.76, No.11, 13 March 1972 (Columbus, Ohio, USA), page 460, column 2, abstract No.59509v, SNIDER, R.H. et al.: "Friedel-Crafts reaction with 5-arylidene-4-thiazolidinones", Int. J. Sulfur Chem., Part A 1971, 1(3), 191-6 (Eng).	1

☒ Further documents are listed in the continuation of Box C.
 ☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 01 March 1996 (01.03.96)	Date of mailing of the international search report 15 March 1996 (15.03.96)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hammer Telephone No. 1/5337058/44

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 95/00183

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chemical Abstracts, Vol.92, No.13, 31 March 1980 (Columbus, Ohio, USA), page 653, column 2, abstract No.110910d, PANDYA, U.H. et al.: "Studies on thiazolidinones. Part VII", J. Inst. Chem. (India) 1979, 51(3), 129-30 (Eng).	8
Y	Chemical Abstracts, Vol.114, No.23, 10 June 1991 (Columbus, Ohio, USA), page 870, column 2, abstract No.229205r, DUNN, A.D. et al.: "Sulfur analogs of deoxyvasicinone. Part 5. Synthesis of methylated analogs", Z. Chem. 1990, 30(8), 288-9 (Eng).	8
Y	Chemical Abstracts, Vol.113, No.11, 10 September 1990 (Columbus, Ohio, USA), page 411, column 2, abstract No.94650p, PISCOPO, E. et al.: "Studies on heterocyclic compounds: 1,3-thiazolidin-4-one derivatives. IV. Biological activity of variously substituted 2,3-diaryl-1,3-thiazolidin-4-ones", Boll.-Soc. Ital. Biol. Sper. 1989, 65(9), 853-9 (Eng).	8
Y	EP 0 316 723 A1 (HOECHST-ROUSSEL) 24 May 1989 (24.05.89), example 5.	8
A	Chemical Abstracts, Vol.109, No.25, 19 December 1988 (Columbus, Ohio, USA), page 847, column 2, abstract No.230870g, SINGH, H. et al.: "Intramolecular chemo-selective heterocyclization of 4-oxothiazolidin-5-yl N-aryldithiocarbamates to fungitoxic 1,3-dithiolo-, 1,3-oxathio-, and thiazolothiazoles", Indian J. Chem. Sect. B 1987, 26B(12), 1200-2 (Eng).	7
A	Chemical Abstracts, Vol.112, No.9, 26 February 1990 (Columbus, Ohio, USA), page 785, column 1, abstract No.77014w, ZALESKA, B. et al.: "Substitution reactions of 2-(aroylmethylidene)thiazolidin-4-one derivatives", J. Prakt. Chem. 1989, 331(1), 55-60 (Eng).	7
A	Chemical Abstracts, Vol.84, No.25, 21 June 1976 (Columbus, Ohio, USA), page 566, column 2, abstract No.180117j, ASTIK, R.R. et al.: "Studies on thiazolidinones, Part I", J. Indian Chem. Soc. 1975, 52(11), 1071-2 (Eng).	8
A	Chemical Abstracts, Vol.85, No.7, 16 August 1976 (Columbus, Ohio, USA), page 521, column 2, abstract No.46484u, ASTIK, R.R. et al.: "Studies on thiazolidinones, Part II", J. Indian Chem. Soc. 1976, 53(3), 272-3 (Eng).	8

Information on patent family members

International application No.

PCT/KR 95/00183

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